

ID AAY02861 standard; protein: 15 AA.

XX AAY02861;

XP-002356219

D5

DT 11-JUN-1999 (first entry)

DE Fragment of human secreted protein encoded by gene 73.

KW Human; secreted protein; fusion protein; gene therapy; protein therapy;  
 KW diagnosis; tissue; cancer; tumour; neurodegenerative disorder; leukaemia;  
 KW developmental abnormality; foetal deficiency; blood; allergy; renal;  
 KW immune system; asthma; lymphocytic disease; brain; hepatic; lymphoma;  
 KW inflammation; ischaemic shock; Alzheimer's disease; restenosis; AIDS;  
 KW cognitive disorder; schizophrenia; prostate; obesity; osteoclast; thymus;  
 KW osteoporosis; arthritis; testis; lung; thyroiditis; thyroid; digestion;  
 KW endocrine; metabolism; regulation; malabsorption; gastritis; neoplasm.

OS Homo sapiens.

PN W09902546-A1.

PD 21-JAN-1999.

PF 07-JUL-1998; 98WO-US013684.

PR 08-JUL-1997; 97US-0051916P.

PR 08-JUL-1997; 97US-0051918P.

PR 08-JUL-1997; 97US-0051919P.

PR 08-JUL-1997; 97US-0051920P.

PR 08-JUL-1997; 97US-0051925P.

PR 08-JUL-1997; 97US-0051926P.

PR 08-JUL-1997; 97US-0051928P.

PR 08-JUL-1997; 97US-0051929P.

PR 08-JUL-1997; 97US-0051930P.

PR 08-JUL-1997; 97US-0051931P.

PR 08-JUL-1997; 97US-0051932P.

PR 08-JUL-1997; 97US-0052732P.

PR 08-JUL-1997; 97US-0052733P.

PR 08-JUL-1997; 97US-0052793P.

PR 08-JUL-1997; 97US-0052795P.

PR 08-JUL-1997; 97US-0052803P.

PR 18-AUG-1997; 97US-0055684P.

PR 18-AUG-1997; 97US-0055722P.

PR 18-AUG-1997; 97US-0055723P.

PR 18-AUG-1997; 97US-0055947P.

PR 18-AUG-1997; 97US-0055948P.

PR 18-AUG-1997; 97US-0055949P.

PR 18-AUG-1997; 97US-0055950P.

PR 18-AUG-1997; 97US-0055953P.

PR 18-AUG-1997; 97US-0055954P.

PR 18-AUG-1997; 97US-0055964P.

PR 18-AUG-1997; 97US-0055984P.

PR 18-AUG-1997; 97US-0056360P.

PR 12-SEP-1997; 97US-0058660P.

PR 12-SEP-1997; 97US-0058661P.

PR 12-SEP-1997; 97US-0058664P.

PR 12-SEP-1997; 97US-0058785P.

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PA (HUMA-) HUMAN GENOME SCI INC.

XX

PI Fischer CL, Rosen CA, Soppet DR, Ruben SM, Kyaw H, Li Y, Zeng Z;

PI Lafleur DW, Moore PA, Shi Y, Olsen HS, Ebner R, Brewer LA;

XX

DR WPI; 1999-120770/10.

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PT New isolated human genes and the secreted polypeptides they encode -

PT useful for diagnosis and treatment of e.g. cancers, neurological

PT disorders, immune diseases, inflammation or blood disorders.

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PS Disclosure: Page 89; 464pp; English.

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CC This sequence represents a fragment of a secreted human protein encoded  
 CC by the nucleic acid molecule detailed in the descriptor line. The gene  
 CC can be used to generate fusion proteins by linking to the gene to a human  
 CC immunoglobulin Fc portion (e.g. AAX27302) for increasing the stability of  
 CC the fused protein as compared to the human protein only. The invention  
 CC relates to 123 novel genes and their fragments (nucleic acid sequences:  
 CC AAX27311-X27449; amino acid sequences AAY02650-Y02788) which are useful  
 CC for preventing, treating or ameliorating medical conditions e.g. by  
 CC protein or gene therapy. Also, pathological conditions can be diagnosed  
 CC by determining the amount of the new polypeptides in a sample or by  
 CC determining the presence of mutations in the new polynucleotides.  
 CC Specific uses are described for each of the 123 polynucleotides, based on  
 CC which tissues they are most highly expressed in (see AAX27311 for  
 CC described uses)

XX

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>C07H 21/04, C12N 15/63</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/02546</b> <b>(43) International Publication Date:</b> 21 January 1999 (21.01.99)																																																																																																
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <b>(21) International Application Number:</b> PCT/US98/13684  <b>(22) International Filing Date:</b> 7 July 1998 (07.07.98)    <b>(30) Priority Data:</b> <table style="width: 100%; border-collapse: collapse;"> <tr><td style="width: 30%;">60/051,926</td><td style="width: 40%;">8 July 1997 (08.07.97)</td><td style="width: 30%;">US</td></tr> <tr><td>60/051,929</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/052,793</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,925</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,931</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,932</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/052,803</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/052,732</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,916</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,930</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,918</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,920</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,919</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/051,928</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/052,795</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/052,733</td><td>8 July 1997 (08.07.97)</td><td>US</td></tr> <tr><td>60/055,948</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,722</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,723</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,949</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,964</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,947</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> </table> </div> <div style="width: 50%;"> <table style="width: 100%; border-collapse: collapse;"> <tr><td style="width: 30%;">60/055,950</td><td style="width: 40%;">18 August 1997 (18.08.97)</td><td style="width: 30%;">US</td></tr> <tr><td>60/055,953</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/056,360</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,684</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,984</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/055,954</td><td>18 August 1997 (18.08.97)</td><td>US</td></tr> <tr><td>60/058,785</td><td>12 September 1997 (12.09.97)</td><td>US</td></tr> <tr><td>60/058,664</td><td>12 September 1997 (12.09.97)</td><td>US</td></tr> <tr><td>60/058,660</td><td>12 September 1997 (12.09.97)</td><td>US</td></tr> <tr><td>60/058,661</td><td>12 September 1997 (12.09.97)</td><td>US</td></tr> </table> </div> </div> <div style="margin-top: 20px;"> <b>(71) Applicant (for all designated States except US):</b> HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).  <b>(72) Inventors; and</b>  <b>(75) Inventors/Applicants (for US only):</b> FISCHER, Carrie, L. [US/US]; 5810 Hall Street, Burke, VA 22015 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). SOPPET, Daniel, R. [US/US]; 15050 Stillfield Place, Centreville, VA 22020 (US). RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US). KYAW, Hla [MM/US]; 520 Sugarbush Circle, Frederick, MD 21703 (US). LI, Yi [CN/US]; 1247 Lakeside #3034, Sunnyvale, CA 94086 (US). ZENG, ZhiZhen [CN/US]; 13950 Saddleview Drive, Gaithersburg, MD 20878 (US). LAFLEUR, David, W. [US/US]; 1615 Q. Street, N.W. #807, Washington, DC 20009 (US). MOORE, Paul, A. [GB/US]; Apartment 104, 1908 Holly Ridge Drive, Mclean, VA 22102 (US). SHI, Yanggu [CN/US]; 437 West Side Drive, Gaithersburg, MD 20878 (US). OLSEN, Henrik, S. [DK/US]; 182 Kendrick Place #24, Gaithersburg, MD 20878 (US). EBNER, Reinhard [DE/US]; 9906 Shelburne Terrace #316, Gaithersburg, MD 20878 (US). BREWER, Laurie, A. [US/US]; 14920 Mt. Nebo Road, Poolesville, MD 20837 (US).  <b>(74) Agents:</b> BROOKES, A., Anders et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, NMD 20850 (US).    <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).       </div>			60/051,926	8 July 1997 (08.07.97)	US	60/051,929	8 July 1997 (08.07.97)	US	60/052,793	8 July 1997 (08.07.97)	US	60/051,925	8 July 1997 (08.07.97)	US	60/051,931	8 July 1997 (08.07.97)	US	60/051,932	8 July 1997 (08.07.97)	US	60/052,803	8 July 1997 (08.07.97)	US	60/052,732	8 July 1997 (08.07.97)	US	60/051,916	8 July 1997 (08.07.97)	US	60/051,930	8 July 1997 (08.07.97)	US	60/051,918	8 July 1997 (08.07.97)	US	60/051,920	8 July 1997 (08.07.97)	US	60/051,919	8 July 1997 (08.07.97)	US	60/051,928	8 July 1997 (08.07.97)	US	60/052,795	8 July 1997 (08.07.97)	US	60/052,733	8 July 1997 (08.07.97)	US	60/055,948	18 August 1997 (18.08.97)	US	60/055,722	18 August 1997 (18.08.97)	US	60/055,723	18 August 1997 (18.08.97)	US	60/055,949	18 August 1997 (18.08.97)	US	60/055,964	18 August 1997 (18.08.97)	US	60/055,947	18 August 1997 (18.08.97)	US	60/055,950	18 August 1997 (18.08.97)	US	60/055,953	18 August 1997 (18.08.97)	US	60/056,360	18 August 1997 (18.08.97)	US	60/055,684	18 August 1997 (18.08.97)	US	60/055,984	18 August 1997 (18.08.97)	US	60/055,954	18 August 1997 (18.08.97)	US	60/058,785	12 September 1997 (12.09.97)	US	60/058,664	12 September 1997 (12.09.97)	US	60/058,660	12 September 1997 (12.09.97)	US	60/058,661	12 September 1997 (12.09.97)	US
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Published With international search report.																																																																																																		
<b>(54) Title:</b> 123 HUMAN SECRETED PROTEINS <b>(57) Abstract</b> <p>The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>																																																																																																		

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123 HUMAN SECRETED PROTEINS  
123 PROTEINES HUMAINES SECRETEES

International Publication Date: January 21, 1999 (19990121)

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Language: English

Attorney/Agent: BROOKES, A., Anders; Human Genome Sciences, Inc., 9410 Key West Avenue, (US).

## ABSTRACT:

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding

regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

La présente invention concerne de nouvelles protéines humaines sécrétées, ainsi que les acides nucléiques isolés renfermant les régions codantes des gènes codant pour ces protéines. L'invention concerne également des vecteurs, des cellules hôtes, des anticorps, et des procédés de production par recombinaison de ces protéines humaines sécrétées. L'invention concerne enfin des procédés diagnostiques et thérapeutiques utiles pour diagnostiquer et traiter les dysfonctionnements liés à ces nouvelles protéines humaines sécrétées.

**Human Secreted Proteins Field of the Invention** This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

**Background of the Invention** Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum 15 (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

**Summary of the Invention** The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

**Detailed Description Definitions** The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original 15 environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the



extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence.

Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 @tg/nil denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1 x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions.

Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1 X SSPE, 0.1 % SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSQ).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such as any Yterminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA

or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatic, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art.

Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslational natural processes or may be made by synthetic methods.

Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine.

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W.

H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1- 12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).) "SEQ ID NO:X" refers to a polynucleotide sequence while "1 SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25- fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.) Polynucleotides and Polypeptides of the Invention FEATURES OF PROTEIN ENCODED BY GENE NO: 1 This gene maps to chromosome 12, and therefore, may be used as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, damage to the cerebellum or additional CNS tissues caused by insults such as trauma or ischemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system (CNS), expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neural cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy

tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 150 as residues: Pro-7 to Cys-21, Leu-25 to Ser The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons 1 5 Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia.

paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo - particularly those associated with neuromuscular junctions, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO: 11, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 11, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 2** This gene is expressed primarily in PHA stimulated T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, autoimmune disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., immune cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 12 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1576 of SEQ ID NO: 12, b is an integer of 15 to 1590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3 The translation product of this gene was shown to have homology to the human retrovirus-related reverse transcriptase pseudogene (See Genbank Accession No.

pirIA253131GNHULI). In specific embodiments, polypeptides of the invention comprise the amino acid sequence.

STHASVQKKDLTKFSAHSWLKKKKKTFRKMIMEEIFLNLIK 1 5 (SEQ ID NO:289), VRSEKGFDKIQCPFMVK (SEQ ID NO:290), FSKPSSYKTYIPKINLHF YILLMNIWETIKIVPLNNCF-rKMNYLGI (SEQ ID NO: 29 1), KKETKLSLFANDMI (SEQ ID NO: 292), and/or SPLLFNILLEVLSSAVRKEKELK (SEQ ID NO:293). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in PHA activated T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and autoimmune diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 152 as residues: Ile- 14 to Thr The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Alternatively, the homology to a reverse transcriptase human gene may implicate this gene as providing utility in the understanding of host-viral interactions, particularly 1 5 those involving retroviruses and other integration-dependent viruses. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO: 13, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4 The translation product of this gene shares sequence homology with npdcf- I which is thought to be important in promoting the survival of bi-potential glial progenitor cells (See Genbank Accession No. gil456107). In specific embodiments, polypeptides of the invention comprise the amino acid sequence.

LRRPSTPLRRPWHLHLQLPRISLGDQRLAQAEMYHYQHQR KELDTALRMRRMRRTETS  
RCTSARAWPRPGKWRCATICSTTPHCPRPC RPPAHLRH CHDLEADRRPLAPR (SEQ ID NO:294),  
RATQGAGHGSSDEENED GDFIFVYECPGM APTGEMEVRNHLFD HAALSAPLPAPSSPLALP (SEQ ID  
NO.295), KAEYATAK ALATPAATPDLAWGPAWGTERGDVPLPAPTATDV VPGAA (SEQ ID NO:296), SAEM  
YHYQHQRQQML (SEQ ID NO:297), LERHKEPPKEL (SEQ ID NO:298), AKCPPGA HACGP (SEQ ID NO:299),

PVHMSPLEP (SEQ ID NO:300), WCRLQREIRLTQ (SEQ ID NO:301), SSDEENEDGDFrVYECPP (SEQ ID NO:302), APTGEMEVNR (SEQ ID NO:303), and/or CPGLSDCALK (SEQ ID NO:304). Additional embodiments are the polynucleotides encoding these polypeptides.

It has been discovered that this gene is expressed primarily in cerebellum and synovial sarcoma and to a lesser extent in several other cancer cell lines.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors characterized by cells of a relatively undifferentiated state, and/or neural tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the synovial fluid, prostate, breast and uterus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neural cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 153 as residues: Pro-6 to Arg- 1 1, Glu-52 to Gly The tissue distribution and homology to npdcf- 1 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating tumors that contain relatively undifferentiated cells. In addition, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Alternatively, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular the connective tissues (e.g., arthritis, trauma, tendonitis, chondromalacia and inflammation). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 14 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 128 of SEQ ID NO: 14, b is an integer of 15 to 142, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 14, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 5** This gene is expressed primarily in colon, pituitary, and to a lesser extent in fetal lung and fibrosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine disorders effecting the Gut/ pituitary/hypothalamic axis.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system and regulation of feeding, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., gastrointestinal tissue, endocrine tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 154 as residues: Asn-26 to Cys-32, Cys- 100 to Leu- 1 12, Cys-128 to Ser- 1 35.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating disorders related to the intake and utilization of food since this gene is expressed in the digestive tract and a CNS site involved in regulation of weight homeostasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these 10 sequences are related to SEQ ID NO: 15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the 15 general formula of a-b, where a is any integer between 1 to 1020 of SEQ ID NO: 15. b is an integer of 15 to 1034, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 15, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 6** The translation product of this gene shares sequence homology with Cortical granule lectin which is thought to be important in blocking polyspermy during fertilization of the egg (See Genbank Accession No. gnlIPID1e I 181610). Preferred polypeptides comprise the following amino acid sequence: RSCKEIKD (SEQ ID NO:305), GGGWTLVASVHEN (SEQ ID NO:306), ADYPEGDGNWANYNTFGSA (SEQ ID NO:307), ATSDDYKNPGYYDI (SEQ ID NO:308), CIGGGGYFPEA (SEQ ID NO:309), and/or EITEAAVLLFY (SEQ ID NO:310). Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in benign and metastatic colon, and to a lesser extent in HEL cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, or inflammatory conditions of the colon. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., gastrointestinal tissue, and proliferating, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 155 as residues: Arg- 15 to Ser-33, Pro- 35 to Cys The tissue distribution and homology to cortical granule lectins indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating disorders of the colon. These may include diseases related to damage or chronic inflammation as well as tumors of the colon. The product may also be useful for the identification of colon cancer metastasis and, as a secreted protein, may have diagnostic and prognostic applications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1184 of SEQ ID NO: 16, b is an integer of 15 to 1198, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 16, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 7** This gene is expressed primarily in eight week human embryos.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fetal and/or developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes anti for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., developing and/or

differentiating cells or tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for detecting embryonic abnormalities. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide 15 sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1433 of SEQ ID NO: 17, b is an integer of 15 to 1447, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 17, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 8** This gene is expressed primarily in endothelial cells. and to a lesser extent in lymph node, tonsils, heart and spinal cord.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular disease such as restenosis, including disorders of the integumentary system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., integumentary tissue, lymph tissue and other cells and tissue of the immune system, cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating diseases of the vasculature including problems associated with diabetes and restenosis following angioplasty. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through 15 sequence databases. Some of these sequences are related to SEQ ID NO: 18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1408 of SEQ ID NO: 18, b is an integer of 15 to 1422, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 18, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 9** The translation product of this gene was shown to have homology to the Gcap I gene product of *Mus musculus*, which is specifically expressed in cerebellum and appears to be developmentally regulated (See Genbank Accession No. gil862343).

This gene is expressed primarily in fetal lung and endothelial cells and to a lesser extent in astrocytes and fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endothelial cell proliferation as in restenosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this



gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., developmental tissue, neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal brain, in addition to the homology to a brain-specific regulatory protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS.

psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating abnormal proliferation of endothelial cells such as occurs upon injury to the lung or arteries. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1093 of SEQ ID NO: 19, b is an integer of 15 to 1107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 19, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 10** This gene maps to chromosome 12, and therefore, may be used as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in infant brain and fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities during gestation such as spina bifida.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in I O providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., developing and/or differentiating cells and tissue, and nervous tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS.

psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.



Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1169 of SEQ ID NO:20, b is an integer of 15 to 1183, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 11** This gene is expressed primarily in fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal failure, tumors of the kidney, and/or developmental abnormalities associated with the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., urological tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 160 as residues: Gln-26 to Gln The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders, particularly renal disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation.

Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1406 of SEQ ID NO:21, b is an integer of 15 to 1420, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 12** This gene is expressed primarily in breast, fetal kidney, and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions: autoimmune disease, chronic inflammatory conditions, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 161

as residues.

His-2 to Lys-7, Ser-28 to Glu The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer e.g., by boosting immune responses. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor I 0 marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1561 of SEQ ID NO:22, b is an integer of 15 to 1575, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 13** This gene is expressed primarily in the frontal cortex of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders, ischemia, Alzheimer's, Parkinson's.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 162 as residues: Glu-31 to Gly The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and 1 5 accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 527 of SEQ ID NO:23,

b is an integer of 15 to 541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 14** This gene maps to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in ovary and to a lesser extent in infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions: cancers and other diseases of the female reproductive system including ovarian cysts and hormonal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, neural cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 163 as residues: Ser-32 to Glu The tissue distribution in ovarian tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of ovarian tumors, in addition to other tumors where expression has been indicated.

Protein, as well as, antibodies directed against the protein may show utility as a tissue- specific marker and/or immunotherapy target for the above listed tissues. Alternatively, expression within the fetal brain indicates that the protein product of this gene is useful 1 5 for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 819 of SEQ ID NO:24, b is an integer of 15 to 833, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 15** The translation product of this gene was shown to have homology to the highly conserved ras gene which is known to be important in the regulation of cell growth, and thus has been shown to serve as an inducible oncogene in eukaryotic tissues (See Genbank Accession No. gb1Z 1 1804IDDRASX). When tested against PC 12 (rat pheochromocytoma cells) cell lines, supernatants removed from cells containing this gene activated the EGRI (early growth response gene 1) pathway. Thus, it is likely that this gene activates sensory neuron cells through the EGR I signal transduction pathway.

The EGR I (early growth response gene 1) is a separate signal transduction pathway from Jaks-STAT, genes containing the EGRI promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases involving immune regulation including autoimmune diseases such as rheumatoid arthritis, lupus, and leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 164 as residues: Ala-28 to His-41, Pro-43 to Gln. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer - particularly considering the homology to a conserved ras gene, combined with the detected EGR1 biological activity. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a 5 nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1541 of SEQ ID NO:25, b is an integer of 15 to 1555, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 16** This gene maps to chromosome 13, and therefore, may be used as a marker in linkage analysis for chromosome 13.

This gene is expressed primarily in kidney cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the kidney including cancer and renal dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., urogenital tissue, and cancerous and wounded tissues) or bodily fluids (e.g., urine, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases of the kidney including kidney failure. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1529 of SEQ ID NO:26, b is an integer of 15 to 1543, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 17** This gene is expressed primarily in T-cell lymphoma and to a lesser extent in bone marrow stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer including lymphomas and leukemias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and bone marrow, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression in bone marrow cells suggest that the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  $a-b$ , where  $a$  is any integer between 1 to 1248 of SEQ ID NO:27,  $b$  is an integer of 15 to 1262, where both  $a$  and  $b$  correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where  $b$  is greater than or equal to  $a + 14$ .

**FEATURES OF PROTEIN ENCODED BY GENE NO: 18** This gene is expressed primarily in a medulloblastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system including cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neural cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 167

as residues: Phe-22 to Leu The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 739 of SEQ ID NO:28, b is an integer of 15 to 753, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19 The translation product of this gene was shown to have homology to the mammalian notch I protein which has been shown to be important in the regulation of cell-fate during pattern formation and development (See Genbank Accession No.

gil57635). One embodiment of this gene comprises polypeptides of the following amino acid sequence:  
KHEXHQVSDGALRCFASLADRFRTRRGVDPAPLAKHGLTEE  
LLSRMAAAGGTVSGPSSACKPXRSTTGAPSTTADSKLSNQ  
SPVVTHTDLLRSELPDSIESALQGDERCVLDTMRLVDFLLV  
RIPGLRRLDSSGERSHRQLIDCIRSKDTDALIDAIDTGAF  
SAFGTQEMVEFLCERGADVNRRGQRSSSLHYAACF  
GRPQVAKTLLRHGANPDLRDEDGKTPDKARERGHSEVVA MCPVNKGDDK (SEQ ID NO:31 1),  
PLDKARERGHSEVVAIL (SEQ ID NO:312), and/or AKTLLRHGANPDLRD (SEQ ID NO: 313). Additional  
embodiments are directed to polynucleotides encoding these polypeptides.

This gene is expressed primarily in endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases involving angiogenic abnormalities including diabetic retinopathy, macular degeneration, and other diseases including arteriosclerosis and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., endothelial cells, and cancerous and WO 99/02546 PCTIUS98/13684 29 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating diseases where an increase or decrease in angiogenesis is indicated and as a factor in the wound healing process. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, considering the homology to the Notch I protein, this gene may show utility in the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related

sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1607 of SEQ ID NO:29, b is an integer of 15 to 1621, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

4:5 FEATURES OF PROTEIN ENCODED BY GENE NO: 20 This gene is expressed primarily in meningioma tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers of the central nervous system and endothelium. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neural cells and tissue, and endothelial, cancerous and FEATURES OF PROTEIN ENCODED BY GENE NO: 21 The translation product of this gene was shown to have homology to the retinoic acid receptor gamma-2 which is thought to be important in development, and may be a key determinant for human breast cancer during aberrant activation (See Genbank Accession No. AA 176435) This gene is expressed primarily in ovary and to a lesser extent in meningioma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, as well as, other cancers of the female reproductive system, and endothelial tissue in general. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 170 as residues.

Leu-8 to Gln-18, Thr-26 to Lys-33, Met-39 to Cys-46, Ala-62 to Pro-69, Pro-83 to Glu The tissue distribution in ovary tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors within these tissues, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tumors and tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2081 of SEQ ID NO:31, b is an integer of 15 to 2095, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 31, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22 This gene is expressed primarily in the spongy tissue from Alzheimer's brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Alzheimer's disease and other neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain



tissues (e.g., neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 171 as residues: Ser-31 to Ala-37, Ala-50 to Tyr Phe-63 to Arg-68, His-83 to Pro The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS; psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1824 of SEQ ID NO:32, b is an integer of 15 to 1838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 23** This gene is expressed primarily in bone marrow cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematological and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e. immune cells and tissue, haematopoietic cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 172 as residues.

Glu-22 to Ser-33, Leu-47 to Ser-55, Thr-87 to Arg The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 768 of SEQ ID NO:33, b is an integer of 15 to 782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 24** This gene is expressed primarily in neutrophils.



Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, haematopoietic cells and tissue, blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 173 as residues: Gln-36 to Lys The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1546 of SEQ ID NO:34, b is an integer of 15 to 1560, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 25** This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, haematopoietic cells and tissue, blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and

committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1078 of SEQ ID NO:35, b is an integer of 15 to 1092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26 This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, hematopoietic cells and tissue, blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 175 as residues: Lys-9 to Leu- 16, Ser-33 to Met The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1139 of SEQ ID NO:36, b is an integer of 15 to 1153, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27 The translation product of this gene was shown to have homology to the intrinsic factor-B 12 receptor precursor of Rattus norvegicus which is thought to be important in development (See Genbank Accession No. gi12961490 (AF022247)). One embodiment of this gene comprises polypeptides of the following amino acid sequence.

DCNRDYLKAFGNLRSPGWPDNYDNDXDCXVTLTAPQNHHS (SEQ ID NO:314), FGNLRSPGWPDNYDN (SEQ ID NO:315), and/or APQNHXLK CRNDFLEV (SEQ ID NO:316). Additional embodiments are directed to polynucleotides encoding these polypeptides.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, haematopoietic cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 971 of SEQ ID NO:37, b is an integer of 15 to 985, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28 This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and/or haematological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,

immune cells and tissue, haematopoietic cells and tissue, blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 177 as residues.

Pro-55 to Ser The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the

natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1108 of SEQ ID NO:38, b is an integer of 15 to 1122, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 29** This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 584 of SEQ ID NO:39, b is an integer of 15 to 598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 30** This gene is expressed primarily in ovarian cancer. This gene also maps to chromosome 7, and therefore can be used as a marker in linkage analysis for chromosome 7.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include,

but are not limited to, ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 115 of SEQ ID NO:40, b is an integer of 15 to 1129, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 31** This gene is expressed primarily in ovarian cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1144 of SEQ ID NO:41, b is an integer of 15 to 1158, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 32** This gene is expressed primarily in ovarian tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the

expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1753 of SEQ ID NO:42, b is an integer of 15 to 1767, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

1 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 33 The translation product of this gene shares sequence homology with uroplakin III which is thought to be important in urothelial differentiation. (See Accession No.

d10226610) Preferred polypeptide fragments comprise the amino acid sequence.

ASIDTWPGRRSGGMIVITSI (SEQ ID NO:317) and/or GSPQAETRWSDPIALHQ  
GKSPASIDTWPGRRSGGMIVITSI (SEQ ID NO:318).

This gene is expressed primarily in ovarian tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to uroplakin III indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:43, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34 The translation product of this gene shares sequence homology with estrogen- 1 5 responsive finger protein. which is thought to be important in uterine implantation. (See Accession No. 1088467; and J. Biol. Chem. 270 (41), 24406-24413 (1995), herein incorporated by reference in its entirety.) Preferred polypeptide fragments comprise the amino acid sequence.

VXDITFDPDTAHKYLRLQEENRKVTNTTPWEHPYPDLPSR (SEQ ID NO:319); LYLHRYFFEVEIFGAGTYV (SEQ ID NO:320); SCISGNNFSW SLQWNGKEFTAW (SEQ ID NO:321); TPLKAGPFWSSGSELTS (SEQ ID NO:322); SVSEVKAVAEMQFGELLA AVRKAQANVMLFLXEKEQAAL (SEQ ID NO:323); EKSKQELETMA AISNTVQFLEEYCKFKNTEDITFPSVYIGLKD (SEQ ID NO:324); LENYKKKLQEF SKEEYDIRTQVSAXVQR (SEQ ID NO:325); and/or GVIYDFPGGELSFYGVVEYDS MTLVHKFACKFSEPVYAA (SEQ ID NO:326). Also preferred are polynucleotide fragments encoding these

polypeptide fragments.

This gene is expressed primarily in ovarian cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer and other disorders of the reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to estrogen-responsive finger protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer and other disorders of the reproductive system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:44, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35 This gene shows sequence homology to a *Caenorhabditis elegans* gene, called D1054 (See Accession No. gnllPIDle348554.) Preferred polypeptide fragments comprise the amino acid sequence.

SKIKYDWYQTESQVVITLMIKNVQKNDVNVEFSEKELSAL  
ELLHPIPEQSTFKVLSTKIEIKLKKPEAVRWEKLEGQGD  
PSSSPYTRNWDKLVGEIKEEEKNEKLEGDAALNRLFQQIY  
AMNKSFMESGGTVLSTNWSVDVGKRKVEINPPDDMIEWKKY (SEQ ID NO:327); GDAALN  
RLFQQIYSDGSDEVKRAMNKSFMESGGTVLSTN (SEQ ID NO:328); and/or DWYQTESQ  
VVITLMIKNVQKNDV (SEQ ID NO:329). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in osteoclastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteoclastoma and other forms of cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of osteoclastoma and other forms of cancers. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related



sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2039 of SEQ ID NO:45, b is an integer of 15 to 2053, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 36** This gene is expressed primarily in Human Placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of embryonic and reproductive systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the embryonic and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of the disorders of embryonic and reproductive systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1258 of SEQ ID NO:46, b is an integer of 15 to 1272, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

**1 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 37** This gene is expressed primarily in Anergic T-cell.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, blood cell disorders, especially those involved with T-cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cells and tissue of the immune system, blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of T cell related disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 759 of SEQ ID NO:47, b is an integer of 15 to 773, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 38** The translation product of this gene shares sequence homology with a murine bone-related sulphatase. (See Accession No. 3046314.) This gene is expressed primarily in retina.



Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, eye diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the eye, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone cells and tissue, retinal cells and other cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 187 as residues: Ala-21 to Arg-27, Asp-40 to Arg-45, Glu-97 to Thr-110, Glu-117 to Lys-128, Arg-175 to Lys-182, Pro-207 to Gly-220, Val-253 to Ile-259. The tissue distribution and homology to sulphatases indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of eye disorders. Moreover, this gene may be involved in bone-related disorders, osteoporosis, Paget's disease, osteomalacia, and diagnosis. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2105 of SEQ ID NO:48, b is an integer of 15 to 2119, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 39** This gene is expressed primarily in human stomach cancers.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly of the gastrointestinal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., gastrointestinal tissue, endothelial cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 189 as residues: Pro-10 to Ser-18. The tissue distribution within synovial tissue indicates the product of this gene may have a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular the connective tissues (e.g., arthritis, trauma, tendonitis).

**FEATURES OF PROTEIN ENCODED BY GENE NO: 40** This gene is expressed primarily in human synovial membrane.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of synovial membrane and musculoskeletal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the synovial membrane system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 189 as residues: Pro-10 to Ser-18. The tissue distribution within synovial tissue indicates the product of this gene may have a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular the connective tissues (e.g., arthritis, trauma, tendonitis).

chondromalacia and inflammation). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST

sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:50, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 41** The translation product of this gene shares sequence homology with adipose specific collagen-like factor as well as the human adipocyte complement related protein Acrp30, the latter of which is known to be important in energy balance and homeostasis involving food intake, particularly in carbohydrate and lipid catabolism. Vanabolism (See Genbank Accession Nos. gnl|PID|d|O08822 and W09108, respectively). In specific embodiments, polypeptides of the invention comprise the amino acid sequence.

XLWDPGLPGVCRCGSIVLKSAFSVGITTSPYEXRLPIIFN R  
GSSSVLSQGIYYFSYDITLANKHLAIGLVHNGQYRIKTFD  
STVIYLQPEDEVWLEIFFTDQNGLFSDPGWADSLFSGFLL DDEL (SEQ ID NO:330), GSIVLKSAFSVGITT  
(SEQ ID NO:331), GIYYFSYDITLA NK (SEQ ID NO:332), DSLFSGFLLYVDT (SEQ ID NO:333), and/or  
NHDVASGST VIYL (SEQ ID NO:334). Additional embodiments are directed to the polynucleotides encoding these polypeptides.

This gene is expressed primarily in human schwannoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurofibroma, and other neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the diseases relating to peripheral or sympathetic nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and locations (e.g., neural cells and tissue, integumentary tissue, extracellular matrix, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 190 as residues: Gly- 16 to Pro-30, Pro- 42 to Gly-56, Gly-62 to Gly-77, Glu-93 to Gly- 104, Glu- 109 to Glu- 114, Pro- 121 to Asp- 126.

The tissue distribution combined with the homology to a conserved human adipose specific collagen-like factor as well as to the human adipocyte complement related protein Acrp30, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders particularly neuroschwannoma, and including Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, considering the homology to a conserved adipose specific collagen-like factor, would suggest that this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type 11, metaphyseal chondrodysplasia type Schmid. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO: 51, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 51, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 42** This gene is expressed primarily in human activated T-Cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiency, and other immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product 15 may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1241 of SEQ ID NO: 52, b is an integer of 15 to 1255, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 52, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 43** This gene is expressed primarily in human activated T-Cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiencies and other immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and cancerous and wounded 15 tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 192 as residues: Glu- 15 to Arg-23, Asn-79 to Gly The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system

disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1126 of SEQ ID NO:53, b is an integer of 15 to 1140, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 44 5** This gene is expressed primarily in human tonsil.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory and immune diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune diseases, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 193 as residues: Ile-2 to Lys-9, Gln-43 to Phe-49, Asn-59 to His-69, Gly-87 to Asp The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1206 of SEQ ID NO:54, b is an integer of 15 to 1220, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45 The translation product of this gene shares sequence homology with a novel human G52-24 secreted protein as well as the early lymphocyte activation antigen CD69, the latter of which has been shown to be important in lymphocyte proliferation and functions as a signal transmitting receptor in lymphocytes, natural killer cells, and platelets (See Genbank Accession Nos. W27288 and gil558352, respectively).

Preferred polypeptides comprise the following amino acid sequence.

ENFLLRYKGPSDHWIGLSREQGQPWKWINGTEWTRQLVMK SQVPRMNPXLS  
WVLLCYPGWSAVXTIVAHCSDLDFPGSK (SEQ ID NO:335), ELTAIK  
SHQYVLQAACPEWIGFQRKCFYFSDDTKNWTSSQRFCDQ VQESFQELVRK (SEQ ID NO:336),  
WIGLSREQGQPWKWING (SEQ ID NO:337), CPESWIG FQRKC (SEQ ID NO:338), NFLLRYKGPSDI-IWIGL  
(SEQ ID NO:339), ASHLRLL SSWDYRFPILGAGECAYLNDKGASSARHYTERKWICKSKSD (SEQ ID NO:340),  
ENFLLRYKGPSDHWIGLSREQGQPWKWINGTEWTRQL VMKEDG  
ANLYVAKVSQVPRMNPXLSWVLLCYPGWSAVXTIVAHCSDL PGSK (SEQ ID NO:341), and/or  
SWTSSLLNXCLHSKEHSIKATIWRLLFFXILTHL CGMVAAALSA  
IRANCHQEPSVCSSSCMRKLDFWFSKKVFLFF (SEQ ID NO:342). Also preferred are the polynucleotides  
encoding these polypeptides.

This gene is expressed primarily in human testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to male reproductive endocrine and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 194 as residues: Asn-20 to Pro-25, Ser-48 to Asp The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Homology of this gene product to the early lymphocyte activation antigen CD69 indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, the tissue distribution within human testis may be indicative of a role for this gene product in normal testicular function, and may implicate this gene product in male fertility, and could even suggest a use as a male contraceptive.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 680 of SEQ ID

NO:55, b is an integer of 15 to 694, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46 This gene is expressed primarily in human testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., endocrine tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g. seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 195 as residues: Pro-20 to Trp-25, Arg- 33 to Thr-38, Asn-51 to Ile-56, Gly-82 to Ser-91, Lys-151 to Arg The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-, hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, expression within the human testis may be indicative of a role for this gene product in normal testicular function, and may implicate this gene product in male fertility, and could even suggest a use as a male contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 974 of SEQ ID NO:56, b is an integer of 15 to 988, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 47 One embodiment of this gene comprises polypeptides of the following amino acid sequence.

LKGREAGAGPGTAGAPGREDANGXXRGRGGXHQLYLWVDN  
RDFS DGVLVAEVIKFYFPMVEMHNYVGTSSLQKLSNWG FSV PDDV (SEQ ID NO:343). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in human adult testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to male reproductive and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., reproductive tissue, and endocrine, cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 196 as residues: Gln-21 to Gly-33, Gln-55 to Glu The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the reproductive system, and may be indicative of a role for this gene product in non-nal testicular function, male fertility, and/or as a male contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker

and/or immunotherapy target for the above listed tissues. . Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1486 of SEQ ID NO:57, b is an integer of 15 to 1500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 48 The translation product of this gene shares sequence homology with the human M phase phosphoprotein 10 as well as ORF YJR002w of *Saccharomyces cerevisiae* (See Genbank Accession No.gnl1PID1e266673). Preferred polypeptides comprise the following amino acid sequence.

AKNSQKEENPEHVEIQKMMDSLFLKLDALSNFHFIPKPPV EE  
VAPVSVSDAALLAPEEIKEKNKAGDIKTA AEKTATDKKRE  
RMKIKEKEKRRKLLLEKSSVDQAGKYSKTVASEKLKQLTKT  
RKLLKGTFVGEVDSKCVWTGMSEPADSPVVG (SEQ ID NO:344), LQDEGKD  
KALKSSQAFFSKLQDQVKMQINDAKKTEKKKKRQDISVH (SEQ ID NO:345), DEGK  
DKALKSSQAFFSKLQDQVKMQINDA (SEQ ID NO:346), EENPEHVEIQKMMDSLFL KLDALSNFHF (SEQ  
ID NO:347), SSVDQAGKYSK TVASEKLKQLTKTGKASFIK (SEQ ID NO:349), VSVSDAALLAPEEIKEK  
NKAGDI (SEQ ID NO:350), and/or SNLPAITMEEVAP (SEQ ID NO:348). Also preferred are the polynucleotides  
encoding these polypeptides.

This gene is expressed primarily in human thyroid.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases relating to the thyroid gland, particularly hyper- and hypothyroidism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., endocrine tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for metabolic disorders, particularly hyper-, hypothyroidism, Graves' disease Hashimoto's thyroiditis, and/or cancer or neoplasias of the thyroid, and/or other endocrine organs and immune system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1377 of SEQ ID NO:58, b is an integer of 15 to 1391, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NOX The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in



SEQ ID NOX These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401 - 450@ 451-500, 501-550, 551-600, 651-700, 701-750@ 751-800, 800- 850, 851-900, 901-950, 951-1000, 1001-1050 1051-1100, 1101-1150@ 1151-1200, 1201-1250, 1251-1300 1301-1350 1351-1400, 1401-1450, 1451-1500@ 1501-1550, 1551-1600 1601-1650 1651-1700 1701-1750@ 1751-1800, 1801-1850@ 1851-1900, 1901-1950 1951-2000, or 2001 to the end of SEQ ID NOA or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NOX or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80 81-100 101-120 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1 - may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1565 of SEQ ID NO:59, b is an integer of 15 to 1579, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 50** The translation product of this gene was shown to have homology to the chicken LRP/alpha macroglobulin receptor which is thought to play a pivotal role on the metabolism of alpha macroglobulins, as well as, complexes between plasminogen activators and their endogenous inhibitors (See Genbank Accession No gb1X749041GGLRPA2MR).

This gene is expressed primarily in neuronal tissues and to a lesser extent in uterine cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neuronal disorders and uterine cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central neuron system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neural cells and tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.



The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered bahaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention.

1 5 Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1227 of SEQ ID NO: 60, b is an integer of 15 to 124 1, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51 This gene is expressed primarily in uterine cancer and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, uterine cancer, and other reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the uterine cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.cy., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.cr., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another Zn tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of the uterus indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or inu-nunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a 1 5 nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 916 of SEQ ID NO:61, b is an integer of 15 to 930, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52 This gene is expressed primarily in Wilm's tumor and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Wilm's tumor, and other urogenital disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Wilm's tumor, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., urogenital tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of Wilm's tumor.

Protein, as well as, antibodies directed against the protein may show utility as a tissue- specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, I 0 preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 984 of SEQ ID NO:62, b is an integer of 15 to 998, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 53** The translation product of this gene was shown to have homology to the MEK kinase 3 of Mus musculus, mutations of which and/or aberrant regulation of, may provide a predisposition to cancer. This gene maps to chromosome 17, and therefore, may be used as a marker in linkage analysis for chromosome 17.

This gene is expressed primarily in pituitary and to a lesser extent in ulcerative colitis, hemapoietic cells, and some other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, gastrointestinal, haematopoeitic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal and immune tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, and cancerous and WO 99/02546 PCTIUS98/13684 68 level, i.e., the expression level in healthy tissue or bodily. fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in ulcerative colitis indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukerru'a. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1 179 of SEQ ID NO: 63, b is an integer of 15 to 1 193, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54 When tested against Jurkat T-cell cell lines, supernatants removed from cels containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates T-cells through the Jaks-STAT signal transduction pathway. GAS (gamma activation site) is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in fetal spleen, adipose, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, metabolic, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal spleen and 1 5 adipose tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., immune cells and tissue, developing cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:203 as residues: Tyr-41 to Phe The tissue distribution combined with the detection of GAS promoter activation activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders.

Expression of this gene product in fetal spleen indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in iminune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and comiruitted progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 816 of SEQ ID NO:64, b is an integer of 15 to 830, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55 This gene is expressed primarily in IL-1/TNF stimulated synovial and human adipose.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, rheumatoid arthritis or obesity. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., synovial and adipose cells and tissues, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID

NO:204 as residues: Leu-37 to Arg-45, Ser-60 to Ser The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or treatment of rheumatoid arthritis or other immune diseases. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 853 of SEQ ID NO:65, b is an integer of 15 to 867, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56 This gene is expressed primarily in aortic endothelium and to a lesser extent in melanocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cardiovascular tissue, and melanocytes, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:205 as residues: Met-1 to Trp-12, Arg-33 to Ser The tissue distribution in human aortic endothelial cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection or intervention of cardiovascular diseases, such as hypertension, cardiovascular injuries, congenital heart diseases, ischemic heart diseases, rheumatic and other hypersensitivity diseases, cardiomyopathy. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 671 of SEQ ID NO:66, b is an integer of 15 to 685, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57 The translation product of this gene shares sequence homology with prostaglandin EP3-9 receptor which is thought to be important in prostaglandin hormonal reaction. In specific embodiments, polypeptides of the invention comprise the sequence:MAIPAFSSCQISSAAALQI (SEQ ID NO: 35 1), and/or CNGPFKHFSFTVST (SEQ ID NO:352). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human retina.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, glaucoma or other ocular diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ocular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., retinal and other optic tissue cells, and tissue of the nervous system, and cancerous and WO 99/02546 PCT/US98/13684 73 prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 787 of SEQ ID NO:67, b is an integer of 15 to 801, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58 The translation product of this gene shares weak sequence homology with Hemophilus influenzae outer protein P6 which is thought to be important in host cell interaction.

This gene is expressed primarily in human adrenal gland tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, adrenal insufficiency or hyperfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., adrenal gland, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in adrenal gland tumor and homology to Hemophilus influenzae outer membrane protein suggest that polynucleotides and polypeptides corresponding to this gene are useful in treating adrenal insufficiencies or hyperfunction because a secretory protein from an endocrine organ may function as a hormone. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 894 of SEQ ID NO:68, b is an integer of 15 to 908, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59 When tested against a Jurkat T-cell line, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates T-cells through the Jaks-STAT signal transduction pathway. The GAS is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a complex, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in human kidney pyramid and to a lesser extent in human brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, nephrotic, nephritic syndromes, renal failure, hypertensive nephrosclerosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., hepatic tissue, brain and other tissue of the nervous system, T-cells and other cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in kidney indicates that polynucleotides and polypeptides corresponding to this gene are useful for renal diseases, including nephrotic, nephritic syndromes, renal failure, hypertensive nephrosclerosis. Additionally, the gene product may have endocrine functions related to renal function, metabolism and homeostasis.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 682 of SEQ ID NO:69, b is an integer of 15 to 696, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 60** This gene is expressed primarily in both normal or cancerous human breast tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Non-neoplastic breast diseases or breast cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., mammary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:209 as residues: Pro-20 to Ser The tissue distribution in breast indicates that polynucleotides and polypeptides corresponding to this gene are useful for either non-neoplastic breast diseases, such as congenital anomalies, gynecomastia, mastitis and abscess, duct ectasia and fat necrosis, or neoplasia in the breast. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 441 of SEQ ID NO:70, b is an integer of 15 to 455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 61** When tested against a K562 kidney cell line, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element) pathway. Thus, it is likely that this gene activates kidney cells through the Jaks-STAT signal transduction pathway. The ISRE is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a complex, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in activated T-cells and osteoarthritis, and to a lesser extent in aortic endothelium, placenta and number of tissues or cell lines.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., T-cells and other cells and tissue of the immune system, bone tissue, endothelium and placenta, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy

tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:210 as residues: Gln-36 to Glu-49, Glu-51 to Leu-66, Asp-68 to Ser. The tissue distribution in activated T-cells and under inflammatory conditions like osteoarthritis suggest that the protein product of this gene is involved in the inflammatory reactions. Therefore it may be useful in the diagnosis or intervention in the inflammatory diseases with the involvement of T-cells, including osteoarthritis.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 399 of SEQ ID NO:71, b is an integer of 15 to 413, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 62** This gene is expressed primarily in breast lymphnodes, B-cell lymphoma and to a lesser extent in neutrophils and bone marrow cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, immunodeficiency, allergy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, hematopoietic cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in the cells of immunological functions indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis or intervention of immunologically mediated disorders, such as allergy, immunodeficiency, immune surveillance, etc. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases.

Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 835 of SEQ ID NO:72, b is an integer of 15 to 849, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 63** The translation product of this gene shares weak sequence homology with Interferon induced 1-8 gene encoded polypeptide which is thought to be important in retroviral REV responsive element binding and thus viral replication.

This gene is expressed primarily in B-cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune response to viral infections and other immunologically related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., B-cells and other cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or



cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:212 as residues: Pro-47 to Asn The tissue distribution in B-cell lymphoma and homology to interferon induced 1-8 gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for intervention of viral infection and other immunologically related disorders.

The homology with interferon induced 1-8 REV response element binding gene indicates the gene product may bind to viral components to interfere with the entry, packaging, replication, or induce the host cell anti-viral response by interferon mediated pathways. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 491 of SEQ ID NO:73, b is an integer of 15 to 505, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64 This gene is expressed primarily in bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hemapoiesis disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemapoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone marrow, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:213 as residues: Thr-45 to Tyr The tissue distribution in bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for hemapoiesis disorders. The gene product may function as a growth factor or mobilization agent for the cells of myeloid or lymphoid lineages. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 705 of SEQ ID NO:74, b is an integer of 15 to 719, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 65 The translation product of this gene shares sequence homology with the familial adenomatous polyposis gene which is thought to be important in tumorigenesis of colon cancer (see, e.g., Fulton, Nature 368, 32-38 (1994); accession no. U28412; Joslyn et al., Cell 66 (3), 601-613 (1991); accession no. M73547; and Spirio et al., Nucleic Acids Res. 19 (22), 6348 (1991)). In specific embodiments, polypeptides of the invention comprise the sequence: CRWRPESAAPC (SEQ ID NO:353), TRPGRGAQAPVK (SEQ ID NO:354), MVSWMISRAVVLVFGMLYPAY (SEQ ID NO:355), GMLYPAYYSYKAVKTKN (SEQ ID NO:356), EYVRVIMMYWIV FALYTV (SEQ ID NO:357), YPAYYSYKAVKTKNVKE (SEQ ID NO:358), VAWFLPYELKIA (SEQ ID NO:359), and/or MVSWMISRAVVLVFGMLYPAY YSYKAVKTKNVKEYVRWMMYWIVFALYTVIETVADQTVAV WLLSPYTKGASLIYRKFLHPLLSSKEREIDDIYVQAKERG AATAAVTAAVKSQGAITERLRSFSMHDLTITQGDPEVQQR PPVN (SEQ ID NO:360). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in osteoclastoma, prostate, bone marrow and to a lesser extent in testes and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, colon cancer and cancers of various origin, including osteoclastoma and prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumorigenesis, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., bone, prostate, bone marrow, colon and other gastrointestinal tissue, tissue of the nervous system, and testis and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:214 as residues: Ser-59 to Ile-64, Ala-71 to Tyr-76, Pro-125 to Ser. The tissue distribution in osteoclastoma, prostate, bone marrow and homology to familial adenomatous polyposis gene indicates polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors of various origins, including colon cancer, osteoclastoma and prostate cancer. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1260 of SEQ ID NO:75, b is an integer of 15 to 1274, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 66** The translation product of this gene shares regional and weak sequence homology with neu differentiation factor and a serine protease N-terminal fragment which contains a EGF-like domain and is thought to be important in growth and differentiation of several cell types, including colon epithelial cells and Schwann cells.

This gene is expressed primarily in fetal lung, bone marrow, fetal liver and to a lesser extent in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tissue injuries or diseases in lung, bone marrow, or liver. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and lung, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., lung and pulmonary tissue, bone marrow, hepatic tissue, neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to neu differentiation factor indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis or intervention of liver or lung injuries, including hepatic failure, recovery from hepatitis, cirrhosis, and complication from liver transplantation. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 505 of SEQ ID NO:76, b is an integer of 15 to 519, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 67** This gene is expressed primarily in activated T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of

the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis, asthma, auto-immune and immunodeficiency diseases.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., T-cells and other cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The expression of this gene in T-cells indicates a potential role in the treatment/detection of immune disorders such as arthritis, asthma, for hypersensitivity reactions and transplant rejection, and also in immune deficiency diseases such as AIDS, and leukemia. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 375 of SEQ ID NO:77, b is an integer of 15 to 389, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 68** This gene maps to chromosome 7, accordingly, polynucleotides of the invention may be used in linkage analysis as a marker for chromosome 7.

This gene is expressed primarily in brain and to a lesser extent in breast.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative conditions and behavioural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., brain and other tissue of the nervous system, mammary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:217 as residues: Leu-40 to His The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 809 of SEQ ID NO:78, b is an integer of 15 to 823, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 69** The translation product of this gene shares sequence homology with a rat secretory carrier membrane protein which is believed to play a role in cell surface re- cycling. See e.g., Brand et al., EMBO J, 1993, Oct; 12(10):3753 Secretory carrier membrane proteins (SCAMPs) are widely distributed as components of post- Golgi membranes that function as recycling carriers to the cell surface. In fibroblasts, SCAMP's are concentrated in compartments involved in the endocytosis and recycling of cell surface receptors while in neurons and other cell types having regulated transport pathways, SCAMPs are also components of regulated carriers (synaptic vesicles, secretion granules and transporter vesicles). Their presence in multiple pathways

distinguishes them from proteins (e.g., recycling cell surface receptors and synaptic vesicle proteins) which are concentrated in selected pathways. The SCAMPs also do not appear to reside beyond the boundaries of these pathways. This distribution indicates that SCAMPs are general markers of membranes that function in cell surface recycling. Accordingly, polypeptides of the invention and antibodies thereto, may be used to identify membranes that function in cell surface recycling.

This gene is expressed primarily in hematopoietic cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:218 as residues: Ser-25 to Gly-31, Gln-149 to Ser-150. The hematopoietic tissue distribution and homology to a cell surface molecule indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of immune or hematopoietic disorders including arthritis, asthma and immunodeficiency diseases. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2441 of SEQ ID NO:79, b is an integer of 15 to 2455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 70** This gene maps to chromosome 4. Accordingly, polynucleotides of the invention may be used in linkage analysis as a marker for chromosome 4. When tested against a Jurkat T-cell line, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates T-cells through the Jaks-STAT signal transduction pathway. The GAS is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a complex, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative conditions and behavioural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:219 as residues: Asp-57 to Gly-58. The tissue distribution of this gene primarily in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior

to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 907 of SEQ ID NO:80, b is an integer of 15 to 921, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 80, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71 This gene is expressed primarily in hematopoietic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, autoimmune and immunodeficiency disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., hematopoietic cells, and cancerous and WO 99/02546 PCT/US98/13684 88 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 81, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 72 This gene is expressed primarily in hematopoietic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, auto-immune and immunodeficiency disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., hematopoietic cells, and cancerous and WO 99/02546 PCT/US98/13684 89 FEATURES OF PROTEIN ENCODED BY GENE NO: 73 The translation product of this gene shares sequence homology with rat synaptogyrin which is thought to be important in membrane trafficking (see e.g., Stenius et al., J. Cell Biol. 131 (6 Pt 2), 1801-1809 (1995)). In specific embodiments, polypeptides of the invention comprise the sequence: QPYQVLPSRQVFALI (SEQ ID NO:361), VFSCI YGEGYSNAHESKQMYCVFN (SEQ ID NO:362), RNEDACRYGSAIGVLAFL (SEQ ID NO:363), LVVDAYFPQISNATDRK (SEQ ID NO:364), and/or SALWTFLWVVGFC FLTNQWAVTNPK (SEQ ID NO:365).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in breast and ovary and to a lesser extent in most hematopoietic tissue types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, female infertility and female reproductive abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., mammary tissue, and ovary and other reproductive tissue, hematopoietic cells and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:222 as residues: Pro-9 to Trp-18, Thr-20 to Ala The tissue distribution in ovary and breast and homology to a protein involved in membrane trafficking indicates that polynucleotides and polypeptides corresponding to this gene play a role in the detection/treatment of female fertility disorders, endocrine disorders, ovarian failure, amenorrhea, ovarian cancer, and also potentially in both non- neoplastic breast diseases such as congenital abnormalities and neoplasia in the breast..

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence

databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1963 of SEQ ID NO: 83, b is an integer of 15 to 1977, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 74** This gene maps to chromosome 12, and therefore polynucleotides of the invention may be used in linkage analysis as a marker for chromosome 12.

This gene is expressed primarily in brain and to a lesser extent in placenta and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, behavioural disorders and neurodegenerative disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, spleen and other cells and tissue of the immune system, placenta, and cancerous and WO 99/02546 PCT/US98/13684 91 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1135 of SEQ ID NO: 84, b is an integer of 15 to 1149, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 84, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 75** When tested against a K562 kidney cell line, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element) pathway. Thus, it is likely that this gene activates kidney cells through the Jaks-STAT signal transduction pathway. The ISRE is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a 15 complex, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in bone marrow and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, autoimmune diseases, transplant rejection and immunodeficiency disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone marrow, cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:224 as residues: Pro-22 to His-33, Ser-42 to Trp The tissue distribution of this gene predominantly in hematopoietic cell types indicates that polynucleotides and polypeptides corresponding to this gene are important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma, immunodeficiency diseases, leukemia, and transplant rejection. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 753 of SEQ ID NO:85, b is an integer of 15 to 767, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 85, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 76 In specific embodiments, polypeptides of the invention comprise the sequence.

SLQYRRUPGRPT (SEQ ID NO:366), DLVTYTSSLQYRIRIPGRPTRP (SEQ ID NO:367), VKTAECYSIPLGSCPVNIRVR (SEQ ID NO:369), and/or LGNKKYIN IRCLEMQVTLKILCEIEKKERRGTHCLV (SEQ ID NO:368). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in primary dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, auto-immune disorders such as asthma and arthritis, in transplant rejection, leukemia and immunodeficiency disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., dendritic cells and other cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:225 as residues.

Gly-2 to Glu-7, Arg-27 to Gly The tissue distribution of this gene predominantly in hematopoietic cell types indicates that polynucleotides and polypeptides corresponding to this gene are important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma, immunodeficiency diseases, leukemia, hypersensitivity and graft rejection. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 714 of SEQ ID NO:86, b is an integer of 15 to 728, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 77 This gene is expressed primarily in 12 week old early stage human.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., developing and/or differentiating cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:226 as residues: Thr-14 to Thr The expression of this gene primarily in the embryo, indicates a key role in embryo development and could be used in the treatment and or detection of developmental disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these



sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 721 of SEQ ID NO:87, b is an integer of 15 to 735, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 87, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 78** This gene is expressed primarily in T-cells, and to a lesser extent in cord blood and osteosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, auto-immune diseases, immunodeficiency diseases and host-graft rejection. Similarly, polypeptides and antibodies directed to these polypeptides, are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., cells and tissue of the immune system, and bone, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:227 as residues: Pro-36 to Ala The expression of this gene in T-cells indicates a potential role in the treatment/detection of immune disorders such as arthritis, asthma, immune deficiency diseases such as AIDS, leukemia and transplant rejection. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 875 of SEQ ID NO:88, b is an integer of 15 to 889, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 88, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 79** This gene is expressed primarily in placenta and 9 week old embryo and to a lesser extent in fetal spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., developing and differentiating tissues, and spleen and other cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The expression of this gene primarily in the embryo, indicates a key role in embryo development and could be used in the treatment and or detection of developmental disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 555 of SEQ ID NO:89, b is an integer of 15 to 569, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 80 This gene is expressed primarily in early stage brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and detection of developmental and neurodegenerative diseases, as well as behavioral or nervous system disorders.

Examples of such conditions would include: depression, schizophrenia, mania, dementia, paranoia, addictive behavior and sleep disorders. In addition a brain-specific gene product may be useful in the diagnosis of specific brain tumors. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 320 of SEQ ID NO:90, b is an integer of 15 to 334, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 81 This gene is expressed primarily in synovial tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis, tendonitis and chondromalacia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the synovium, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of connective tissue disorders such as arthritis, tendonitis, chondromalacia, inflammation and trauma. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 781 of SEQ ID NO:91, b is an integer of 15 to 795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 91, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 82 This gene is expressed primarily in frontal cortex of brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:231 as residues.

Ser-4 to Tyr- 13.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of developmental and neurodegenerative diseases of the brain and nervous system, including malignancies as well as behavioral disorders. Examples of such conditions might include: depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and sleep disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 563 of SEQ ID NO:92, b is an integer of 15 to 577, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 83** The translation product of this gene shares sequence homology with the L6 cell surface antigen, which is highly expressed in lung, breast, colon, and ovarian carcinomas. See e.g., Marken et al., Proc Natl Acad Sci U S A 1992 Apr 15;89(8):3503 In a specific embodiment, polypeptides of the invention comprise the sequence: ITLCLVCIVANA (SEQ ID NO:370). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in tissues of liver origin (fetal liver, hepatoma, hepatocellular tumor).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers of the liver. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., lung and pulmonary tissue, colon and other gastrointestinal tissue, mammary tissue, ovarian tissue and other tissue of the reproductive system, and hepatic tissue, and 15 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:232 as residues.

Asn-32 to Asn-41, Thr- 140 to Ala- 147, Asp- 188 to His- 197.

The murine monoclonal antibody (mAb) L6 recognizes an integral membrane glycoprotein that is highly expressed in lung, breast, colon, and ovarian carcinomas and is referred to as the L6 antigen. This antigen is an attractive target for therapeutic intervention due to its high level expression on malignant cells. The tissue distribution and homology to L6 antigen indicates that the protein product of this gene is useful for detection and treatment of neoplastic tissues -- particularly of the liver. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly

available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 954 of SEQ ID NO:93, b is an integer of 15 to 968, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 84** This gene is expressed primarily in glioblastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, glioblastoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of malignancies, as well as developmental and neurodegenerative diseases of the brain and nervous system.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 539 of SEQ ID NO:94, b is an integer of 15 to 553, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 85** The translation product of this gene shares sequence homology with Tbx which is thought to be important in developmental regulation (see e.g., Knezevic et al., Development 124: 411-419 (1997); accession No. U80951). In specific embodiments, polypeptides of the invention comprise the sequence: VTAYQNQQITRLKIDRNPFAKGFR (SEQ ID NO:371), GTATVTAYQ NQQITRL (SEQ ID NO:372), KIDRNPFAKGFRDSGRNRMGLEAL (SEQ ID NO:373), VESYAFWRPSRLTLTFEDIPGIPKQGNASS (SEQ ID NO:375), and/or STLLQVLGMAFLPLTLTFCLA (SEQ ID NO:374). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in synovial sarcoma and to a lesser extent in osteoclastoma and hemangiopericytoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteosarcoma, osteoclastoma, chondrosarcoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., bone cells and tissue, and synovial cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:234 as residues.

Ala-45 to Asp-50, Arg-57 to Pro The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of osteoporosis, fracture, osteosarcoma, osteoclastoma, chondrosarcoma, ossification and osteonecrosis, arthritis, tendonitis, chondromalacia, inflammation. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 954 of SEQ ID NO:95, b is an integer of 15 to 968, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 86** This gene maps to chromosome 19, accordingly, polynucleotides of the invention may be used in linkage analysis as a marker for chromosome 19. The translation product of this gene is a transmembrane protein that forms disulfide-bonded homodimers and contains a motif in its cytoplasmic domain (located at the carboxy terminus of the protein relative to the transmembrane domain) that functions as an adaptor for associating protein complexes involved in triggering cellular activation. The transmembrane domain is predicted to consist of the amino acid sequence.

VLGIVMGDLVLTVLIALAVYFLG (SEQ ID NO:377). In specific embodiments, polypeptides of the invention comprise, or alternatively, consist of, the sequence.

QAQSDCSCSTVSPG (SEQ ID NO:376), VLAGIVMGDLVLTVLIALA VYFLG (SEQ ID NO:377), VPRGRGAAEATRKQRITETESPYQELQGQRSDVYSDL (SEQ ID NO:378), and/or ETESPYQELQGQRSDVYSDLNT (SEQ ID NO:379).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in macrophages.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunologically mediated disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this Crene Zn at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:235 as residues.

Ala-28 to Ser-33, Ala-76 to Lys-111.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g., AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 683 of SEQ ID NO:96, b is an integer of 15 to 697, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID

NO:96, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 87 This gene is expressed primarily in prostate cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., prostate, and cancerous and WO 99/02546 PCTIUS98/13684 104 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 852 of SEQ ID NO:97, b is an integer of 15 to 866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 88 The translation product of this gene shares sequence homology with retinal epithelial membrane protein (REMP), which is thought to be important in development and maintenance of normal retinal function (See e.g., Philp et al., Exp. Cell Res. 219 (1), 64-73 (1995); and accession no.U15685). The translation product of this gene also shares homology with monocarboxylate transporter protein (accession no.U87627). In specific embodiments, polypeptides of the invention comprise, or alternatively, consist of, the sequence: FLCALSPLGQLLQDRYGWGGFLILGGL (SEQ ID NO:380), LLNCCVCAALMRPLVVTAQPGXGPPRP (SEQ ID NO: 381), and/or SRRLXDLSV FRDRGFVLYAVAASVM (SEQ ID NO:382). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils and to a lesser extent in a variety of other tissues and cell types, including retina.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, eye disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the eye, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., retinal cells and other cells and tissue of the nervous system, neutrophils and other blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder. relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to REMP indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of eye disorders, including neoplasms, visual impairments and blindness. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1354 of SEQ ID NO:98, b is an integer of 15 to 1368, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 89 The translation product of this gene shares sequence homology with human squamous cell E48 antigen which is thought to be important in self-recognition, immune function. Additional embodiments of the invention are directed to polypeptides comprising the sequence.

MMATPSTRPPPPAASTTSATAPALPPRPPWPWPSSWPPS NKAL (SEQ ID NO:383);  
LLTSPLPRCPACSHDAPAHDPGGPHGLTSGPGLG

LPRVCLQRRQLLQPHALPGYGCLLDHAHLLHPHQDEGQ (SEQ ID NO:384); and/or  
WLLQARVHLLLPVRPLQRHRPCHPGHPGPGHPGHPGLG RQTHSR TKLS (SEQ ID NO:385). Further  
embodiments of the invention include polynucleotides encoding these polypeptides.

This gene is expressed primarily in adult brain and to a lesser extent in fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other cells and tissue of the immune system, lung, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:238 as residues: Tyr-28 to Phe-34, Thr-54 to Val-60, Tyr-73 to Thr. The tissue distribution and homology to human squamous cell E48 antigen indicates that the polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of autoimmune diseases and disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 599 of SEQ ID NO:99, b is an integer of 15 to 613, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 90 Additional embodiments of the invention include polypeptides comprising of the following amino acid sequences.

QEFQTGLGNMVKPCLYEKYRNISWLWWHTPVVPATWEAEV (SEQ ID NO:386) and/or  
ILGGESILILSWVFSYIFFRIALEITIYILNVSPFCLG RWLM PVIPALVv'EAEVGGGLPELRSSRPA (SEQ ID NO:387). Further embodiments include polynucleotides encoding these polypeptides.

This gene is expressed primarily in human adult lymph node tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders and lymphomas. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and metabolic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., lymph tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of immune and lymph diseases and disorders such as lymphomas. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 671 of SEQ ID NO: 100, b is an integer of 15 to 685, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 100, and where b is greater than or equal to a + 14.



FEATURES OF PROTEIN ENCODED BY GENE NO: 91 Additional embodiments of the invention include polypeptides comprising of the following amino acid sequences: MPKQLAQLLYRLPRG (SEQ ID NO:388); LFQAIS VSGSHRQGSRTWNTLTEGNAEAACTVALQTSKRLILASRW (SEQ ID NO:389); TLSFMNSHCVPKALFFLSVVSIFIMPHHIFTVKILKS (SEQ ID NO:390); and/or RPTRPITFSSNISEWVPSTGFQDLEHFNRRKCRSS LHSCFTDFQEADSGFKMEPWSWFFFFFFFFFPQRTCGCALC GPHGKELLNSFLYELPLCSYKGPFLS (SEQ ID NO:391). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in placenta and synovium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases of the synovium and placenta.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the placenta and synovium, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial tissue, and cancerous and FEATURES OF PROTEIN ENCODED BY GENE NO: 92 Additional embodiments of the invention include polypeptides comprising the following amino acid sequences.

VDPRVRLPLFWWQPSCAVYLFPRVYNNMCTRVLGTLPHCW WGNVSEAPGM (SEQ ID NO:392); VPYHIAGTLPHCCSLPVGYGGMSVRL QGCRYVGNVGPQGNMQSGRSWALKMVLLCNSCLGLGVGSV GAVLSETPGSSVY (SEQ ID NO:393); and/or MLDPRATCNLVGVGLS KWCCCVTAAWVLG (SEQ ID NO:394). Further embodiments of the invention include polynucleotides which encode these polypeptides.

This gene is expressed primarily in chronic lymphocytic leukemia.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases of immune system including cancer.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of disorders of the immune system including cancers. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 812 of SEQ ID NO: 102, b is an integer of 15 to 826, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 102, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 93 Additional embodiments of the invention include polypeptides comprising of the following amino acid sequences.

HGDWIYVHIVEQLNQANNKSVTSHTYFVVKTKIHSLSNF LYNRSLELELPV (SEQ ID NO:395); TYSSCLTKILYSLINIYPIPHCSPAXITTEL LSASMNLTFFFFRFHICEIAQYLSFCAWLISLNIKSL (SEQ ID NO:396); and/or MNLTFFFFRFHICEIAQYLSFCAWLISLNIKSL (SEQ ID NO:397). Further embodiments

include polynucleotides which encode these polypeptides.

This gene is expressed primarily in brain inedulloblastorna.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of cancer and disorders of the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancers and other disorders and diseases of the CNS. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the 5 general formula of a-b, where a is any integer between 1 to 572 of SEQ ID NO: 103, b is an integer of 15 to 586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 103, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 94 Additional embodiments of the invention include polypeptides comprising the following amino acid sequences.

LVCYCSTKKEKKLHEIAIQQGQNWRWLLFYKEISVPGFQS KAGEGG (SEQ ID NO:398);  
RRSCSGPPLVNTAGKILSSSPAKLACKRTDFHPSI (SEQ ID NO:399);  
RASILGIDNERGCHFRHFNPLKEYKRKKKENKSFRIV (SEQ ID NO:400);  
SKNKTRGGDWCVTVLRKRRKSFMKSPFSKDRDGDGFSFTK  
LSQAFSLFGVHTSVCVLCGRRGKAGEGGPVQGPLW (SEQ ID NO:401); and/or  
MKSPFSKDRDGDGFSFTKKSLSQAFSLFGVHTSVCVLCGR PLW (SEQ ID NO:402). Further embodiments include polynucleotides comprising these amino acid sequences.

This gene is expressed primarily in meningima and neutrophils and to a lesser extent in anergic T cells and CD34 depleted buffy coat.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory, immune and hemopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemopoietic, immune and inflammatory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., T-cells and other cells and tissue of the immune system, meningima, neutrophils and other blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:243 as residues.

Glu-45 to Asn The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis and treatment of various 5 disorders and diseases of the immune, inflammatory, and hemopoietic systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 104 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 614 of SEQ ID NO: 104, b is an integer of 15 to 628, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 104, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 95 Additional embodiments of the invention include polypeptides comprising the following amino acid sequences: MGESECYRRLSGASCTWTVHVDFA (SEQ ID NO:403); MHCGRVWKTMKHDYFLLACLSMTSTGGILCTL (SEQ ID NO:404); STLSLIPTSSSLFWPWCTAIIGSIFTYCVCVCVCFVVMN ATIIDKSMTLS (SEQ ID NO:405); and/or MWILPKVSLICIVELGYGKP (SEQ ID NO:406). Further embodiments include polynucleotides encoding these polypeptides.

This gene is expressed primarily in human meningima.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, meningitis and other inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cerebrospinal membranes, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., meningima, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:244 as residues: Ser-35 to Phe The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment, and diagnosis of disorders of the meningima. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 544 of SEQ ID NO: 105, b is an integer of 15 to 558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 105, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 96 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

MSTGDGRDAEKGWVPVSEENQRSVYPGYPECDERQAVPQH PASACVPRR (SEQ ID NO:407); QQMTLGTKIKWGQLQRGQEPTGDFrVR NFMRFISI IYC (SEQ ID NO:408); and/or PFLFCASRIRXQGIGIHGQ VACSAVRMYNNR (SEQ ID NO:409). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in activated monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hemopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., monocytes and other cells and tissue of the immune system. and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual haviner such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid

from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:245 as residues.

Met-1 to Ser-6, Pro-29 to Ser The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of diseases of the immune and hemopoietic systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 742 of SEQ ID NO: 106, b is an integer of 15 to 756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 106, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 97 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

VLCEEAGQKVPSTPSWSSWTLQKRLRGSPAANCSPSPFA (SEQ ID NO:410); MSLSALACDFT  
PIQPWEWEEYEQITLGLTAPSNLLESNYLGQASECFV  
RKLVRFPQLLPGGHCRKDLGDPQQRPIALLPSLPHQE DL (SEQ ID NO:411);  
CVDFFEYFSSWEPLLKMMFKGVVGGKMKAVRRKKR RKPLPYKIHAD (SEQ ID NO:412); and/or  
MMFKGVVGGKMKAWRRK KRRKPLPYKIHAD (SEQ ID NO:413). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in bone marrow and to a lesser extent in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hemopoietic and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemopoietic and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone marrow, testes and other reproductive tissue, and 15 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of various disorders involving the hemopoietic and reproductive systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 132 of SEQ ID NO: 107, b is an integer of 15 to 146, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 107, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 98 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

LISSVNKTKQKRSDATLSHKHDRLLNHVFFGNSYNY (SEQ ID NO:414); SSKFPS  
DMLLRQIIYCHKLTIELTKWRNTARHKSKKKEDELILK  
KRAAAEESNFPERSSEVFLVDETLKCDISLLPEXAILQV[IYYNLPVV VHACNPSCLLGG (SEQ ID NO:415);  
SLESTNAIKSN (SEQ ID NO:416); IRPNKNDQMRHCLINMIDY (SEQ ID NO:417); ITLCFLETAITINIYSNL  
VNFLQICYCGYNRSSIVTS (SEQ ID NO:418); and/or ISFRYAIAADTTDHLLSQA NHYPNKMAEYSKT (SEQ ID  
NO:419). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in nasal polyps.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., nasal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders of the immune system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 108 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 761 of SEQ ID NO: 108, b is an integer of 15 to 775, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 108, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 99** An additional embodiment of the invention is directed to polypeptides comprising those which exhibit sequence homology with honeybee venom sacepin.

Further embodiments of the invention are directed to polynucleotides which encode these polypeptides. Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

PQIKLLNSDALGMRTTSXDLVPCNQCFIPLPPSCNRIASR GLLNNAPHRRPPTPTPCVFPSEGPCKGYGFHV (SEQ ID NO:420); EQLAXISCR VINVSFRCLHHVIESLPERQLTGSSRGSQP (SEQ ID NO:421); EDCSTMPPI AAPPPLAPLVFSPLRGPRVMAFMSRCGDRGGRGRSXAGRG PKKRPCPGPMLS (SEQ ID NO:422); and/or EFGTRRQWGTR CFPPLVGRKQ SALRRREGKARAGRCCGKRSVKAGFDA (SEQ ID NO:423). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in activated and control neutrophils and to a lesser extent in fetal liver and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of disorders of the immune and endocrine systems.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, inflammatory and hormonal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, spleen and other cells and tissue of the immune system, liver, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, diagnosis and treatment of inflammation and various disorders of the immune and endocrine systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 109 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 897 of SEQ ID NO: 109, b is an integer of 15 to 911, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 109, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 100** 1 0 This gene is expressed primarily in activated neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, inflammation. Similarly, polypeptides and antibodies 15 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g. neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of inflammatory and immune conditions. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 110 and may have been publicly available prior to the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 442 of SEQ ID NO: 110, b is an integer of 15 to 456, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 110, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 101** Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences: ATVPGSIYNYFYHYNAGALKPEHASESPRGLCAQTAGPFP (SEQ ID NO: 424); IRHEPPPPRFKRFSCSLSSWDYRRAPPHVAIFCTLSRD PGWSQTPDLK (SEQ ID NO: 425); STHLGLPRCWDYRHEPLCLAPFTISHIMQ GLSNLSMPQNPPPEGCAHRLDLSPASDSVPPEWGSKI AFE (SEQ ID NO: 426); and/or LRVGGTSENCCRGECGVCIPPGR (SEQ ID NO: 427). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence

databases. Some of these sequences are related to SEQ ID NO: 111 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 540 of SEQ ID NO: 111, b is an integer of 15 to 554, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 111, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 102** This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at 5 significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 251 as residues.

Lys-33 to Lys The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 112 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 708 of SEQ ID NO: 112, b is an integer of 15 to 722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 112, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 103** This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 113 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.



Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 917 of SEQ ID NO: 1 13, b is an integer of 15 to 93 1, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 1 13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 104 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences:GLCMVHSLLTSSLGGRCCNYPYIADKDEETEVK PPSQGHTWHLHCS (SEQ ID NO:428); QLWCITALPSTRHCSKGFAWFrHSLRH PSVAGAVIILELQT RTLRQRSSHLPGKTHGICTAPDRPTERA AVTILK (SEQ ID NO:429); SFDNN NSYGVSQLYQVPD TVLRALHGSLTPYVIPRWQVL (SEQ ID NO:430); and/or DRGQATFP RAHMASALLLTDRQRELLSRSSNELCMSKV (SEQ ID NO:43 1).

Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune diseases and disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 1 14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 574 of SEQ ID NO: 1 14, b is an integer of 15 to 588, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 1 14, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 105 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

LLLELRPFLNSQFKLQLPLVLFHSSCTYICLLYNYELFHI AHHLELAVAHXGCSIPIY (SEQ ID NO:432); and/or THNSNYSSLWFSST AVVLTYYVYYIIMNCFILSPLQVN (SEQ ID NO:433). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum).

plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of inflammatory and immune disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 115 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 798 of SEQ ID NO: 115, b is an integer of 15 to 812, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 115, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 106 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

TLVAGSPCSLSRWIMAGFCHGELVQSDMESQEWERGQVVL R (SEQ ID NO:434);  
MAGFCHGELVQSDMESQEWERGQVVLSTSLPWCYVSPR (SEQ ID NO:435); and/or  
MAVWISGSYSSFCRSRNDVDFSPNIVLASLPFSFRS  
VSKAAKPWWLALPALFPDGLWLD SAMGSLYSQTWKARN GK PHCLGAMSHL (SEQ ID NO:436). Further  
embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:255 as residues: Pro-54 to Gly. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 116 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO: 116, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 116, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 107 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

RSKRQSQGSRCSVPLLAQQRSPVPLQAQPAWLLGSETI DPGTSTAAGNSGPGIGMGHRTPPPSHTGR  
(SEQ ID NO:437); RWDPAWGLD IPSSCPVTMGELRSGDGIVL (SEQ ID NO:438); GALLWDNSMISAPRG  
SHREAGALFPSWLSNPAVLPSRSPSQPGCLDPRQ (SEQ ID NO:439); NSARE  
PRRWIRPTRGSETTAPCCFEPLNGGTLVHAAAMARASEA (SEQ ID NO:440); MARASE AAGTG (SEQ ID  
NO:441); CFrTAFQKALRDPRPTLPDTHG SLRNAPLKSLTLPAAFVVSFFLSLLQDGIKERSQTQ NAT

GLSEEPGSGTTP (SEQ ID NO:442); and/or LALQE AVTGKQVLCSP  
GSAIPQSSRPAPGPASLAAWIRNSLVWRRLRVGGTQGP RDGAQDTPISHREMKVGSSMGTGHP (SEQ ID NO:443). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., neutrophils and other blood cells, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:256 as residues: Met-25 to Gly The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 1 17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO: 1 17, b is an integer of 15 to 75 1, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 1 17, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 108 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

MFYSKIFYFLLNSDTSNNVTSKTLVSSISSNNRLAVSI (SEQ ID NO:444);  
SRQKNLLKLHSPNCDNFCIFNYKPKYICIFKLICKIL (SEQ ID NO:445); and/or  
MLLSLLMVFFSELYVKRHISFKSXDKPHCHKNQDIDVLFRLKHFVKVINMICFP (SEQ ID NO:446). Further  
embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in fetal liver and to a lesser extent in bone and breast cancer cell lines.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., hepatic tissue, bone, mammary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of growth and metabolic disorders and neoplasias. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 1 18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO: 118, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 118, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 109 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences: FREYGFYNLHFC (SEQ ID NO:447); LVTTDYYDGCNEDYEYNWSYMLNSEQLFIFYPTFFC (SEQ ID NO:448); and/or NVIAPGLESSCANSFLFLFVCLPVAHHRHNFLFIKHSLYN HLRDYESDFDKI (SEQ ID NO:449). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in T cells, fetal heart and infant brain and to a lesser extent in some transformed cell lines.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of growth and immune disorders and diseases.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and cardiovascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., T-cells and other cells and tissue of the immune system, heart and vesicular tissue, brain and other tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of developmental and immune disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 119 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1428 of SEQ ID NO: 119, b is an integer of 15 to 1442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 119, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 110 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

PKVLAVLKKKNHVALSIFELLSNDICSFISFFMS (SEQ ID NO:450); EGPDIN  
SNLKFLCLCKKIMWPFQYLNC (SEQ ID NO:451); and/or LLSLILLRIWYD  
FSKQTVFWFLNVFNFFSSCNNDGACSYKYRKVQI (SEQ ID NO:452). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in osteoblasts and to a lesser extent in bone marrow and bladder.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal and hemopoietic diseases and disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and vascular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., bone, bone marrow, and bladder, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:259 as residues: Gly-33 to

Lys The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis, and treatment of bone and hematopoietic disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 120 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are - specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 831 of SEQ ID NO: 120, b is an integer of 15 to 845, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 120, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 111 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences: HTLFISFLWAEG (SEQ ID NO:453); MLPVFVLFFCFTYSARKQSVFKKGNVFE (SEQ ID NO:454); and/or SPCSAA ECHNLSLLS SCSLVSSNILFSFPFFGQKARCCFLFYFSASHIAHESRV KEMCL (SEQ ID NO:455). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in prostate cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate and other cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., prostate, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of prostate cancer and other neoplasias. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 121 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 346 of SEQ ID NO: 121, b is an integer of 15 to 360, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 121, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 112 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

HKCFQCFLANGFLKVIKPFQRNWSDKTFFLVCLNKAISE NLLLETFCTI (SEQ ID NO:456);  
LLGVLKPLYFSVEPVLGERSVAFEEVREKNH GTSGFLSLYSLAAIVCGHLMFFHTLLGRGGNDHPGQSPLP  
AGQAPSGHPWMQPLDTCLL (SEQ ID NO:457); RPTRPPTRPDRPSLELAPG  
LCADFLGSSNHCIIFLLSLYLGRDQ (SEQ ID NO:458); and/or EKRIMVPQGF  
FPFTRWQPLSVGTSCFSTLYWAVEVTITQASLLCLGCAL (SEQ ID NO:459).

Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in haemopoietic and neural tissues and to a lesser extent in a number of cancers and other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include,

but are not limited to, diseases of the haemopoietic and neural systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and neural system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., haematopoietic tissue, and neural cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the haemopoietic and neural systems including several cancers. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 122 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 930 of SEQ ID NO: 122, b is an integer of 15 to 944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 122, and 10 where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 113** The translation product of this gene shares sequence homology with intestinal epithelium proliferating cell-associated mRNA sequence which is thought to be important in growth and development of epithelial cells. Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

MTLDEWKNLQEQRPKPEFNIRKPESTVPSKAVVIRESKY  
HVFRKPANDITSQLEINFGNLPRPGRGARGGTRGGRGRIR QDVAPNPDDPEDFPALS (SEQ ID NO:460);  
CKMLPPTQMTRKISLRCLERALFP STAELHCTPVGRLFQLGQGSQTLRTIDVAFPVSCKFVALF  
QRLESRPFPKMKNGDCVFEEGISNEE (SEQ ID NO:461); PPSSWAWS  
QRRHPGRPGKDQEGRELWTQSRSGDARCCPQPR (SEQ ID NO:462); and/or  
CLKCVYRDSIDSSAEAWRERRL (SEQ ID NO:463). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in brain and central nervous system and to a lesser extent in testis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the neural system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., brain and other cells and tissue of the nervous system, testis and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:262 as residues: Glu-20 to Glu-27, Glu-30 to Trp. The tissue distribution and homology to intestinal epithelium proliferating cell-associated mRNA sequence indicates that polynucleotides and polypeptides corresponding to this gene are useful for growth and developmental diseases of the brain, central nervous system and reproductive system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 123 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 900 of SEQ ID NO: 123, b is an integer of 15 to 914, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 123, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 114 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences: LSYSVLLILP LFHSLPTL KDTHTHNKWVE (SEQ ID NO:464); EVNGVGYKESCFSDISSVLENKDS RMRAPHYASFQHFVLLKLSPQACLTESQCIPLTFY (SEQ ID NO:465); KTHHTISGWSKKSTELDISIP AFLTSPVSWRTRILE (SEQ ID NO:466); and/or IRHELGSDDPPAEASQIAGTAAVSHHAQP (SEQ ID NO:467). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in spinal cord.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, spinal cord injuries and diseases of the neural system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., spinal cord and other cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:263 as residues.

Pro-45 to Gln The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of spinal cord injuries and diseases of the neural system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 124 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 448 of SEQ ID NO: 124, b is an integer of 15 to 462, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 124, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 115 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences: MLYLELISLSSLSFSFSLPPFSIII (SEQ ID NO:468); SSYFLRHFRITYHTCPKYFSMNIIN (SEQ ID NO:469); KLTLTGKNSWSSTAVAAALELVDPPGCRNSARDSLPNST MFYYAC FIFYSSLSPSLSLSPSLLSLL (SEQ ID NO:470); and/or QFHTGNSYDHDYAK (SEQ ID NO:471). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in striatum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of a number of diseases of the neural system.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural diseases, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., striatum, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the neural system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 125 and may have been publicly available prior to conception of the present invention. Preferably, such related



polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 531 of SEQ ID NO: 125, b is an integer of 15 to 545, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 125, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 116 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

AVCTGGGYCESCRCEHCVCVCVDLCVLFSGKELRVR (SEQ ID NO:472); VSFFFV  
FKWSFAEIKSREEHWASLTPKPTLLSALLTCDVLKSSIIF QASKDGSSSRI (SEQ ID NO:473); RSWGS  
QRSCLLLFIPFAAESYSVVWMGHL FVVCLSSWWTFRPFALAVTVNHVAVNIVCVSAWTCVSCS  
PLETLWFPHMVVLCLTF (SEQ ID NO:474); GHLFVVCLSSWWTFRPFALAVT  
VNHVAVNIVCVSAWTCVSCSLGRSCGLEGSFLFPLETLWF (SEQ ID NO:475);  
HDVLGARNAACVCCSFLQQNRELLFGWATCLLSVYSPA GGHLGR LHWRL (SEQ ID NO:476);  
MLDFKTSQVSKALKRVGFGVRLAQ CSSLDLISAKLHLKTKKKETYITSTVMTAASLFLSYVTSE  
KLHIGEMGTLQTAGGSKMTWPLQKAIWQFLKRLSIKLPYV (SEQ ID NO:477); and/or  
LTRNSFPENRTHKSTQHTQCSQRHDSQ (SEQ ID NO:478). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in intestine and cancer cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the gastrointestinal tract and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., gastrointestinal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or 15 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of diseases of the digestive system and cancer. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 126 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 898 of SEQ ID NO: 126, b is an integer of 15 to 912, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 126, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 117 The translation product of this gene shares sequence homology with a human apoptosis regulating protein which is thought to be important in regulating cell death.

Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

IRHEGQSSSRGSSSHCDSPSPQEDGQIMFDVEMHTSRDHSS  
ALKKSADWVSDWSSRPENIPPKEFHRHPKRSVSLS (SEQ ID NO:479);  
GILLTLYPFWPEDILEFPNRVYCCLEICKGFFSANATSL (SEQ ID NO:480);  
EFGTRDRVVPEAVLTVTALRHKKMGRSCLMWKCTPAGTIA (SEQ ID NO:481);  
AHPLPAPTEGKEKPLEMRVTCEVVYCHSSLFELETIVSMT LFLHIQFQ (SEQ ID NO:482);  
TFCVFKHEEKWSHEERGYFLRRISEGVHSISLPF SCFGFGARHLYWKATEHTLCQHLLRERKSPWKCV

(SEQ ID NO:483); and/or QSLLFRNLQGLLFRKCHQQHLSAMLLSLISATRLDLYH TTISLLKRDQVSK (SEQ ID NO:484). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in muscle, fibroblast cells, haernopoietic cells, fetal lung and to a lesser extent in several other tissues and cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the haernopoietic, muscular and developing system.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and muscular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., muscle, fibroblast and other cells and tissue of the nervous system, haernotopoietic cells, and lung, and cancerous and wounded tissues) or bodily fluids (e.cr., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:266 as residues.

Met- I to Ala The tissue distribution and homology to apoptosis regulating protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the haernopoietic, muscular and developing system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 127 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1034 of SEQ ID NO: 127, b is an integer of 15 to 1048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 127, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 118 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences: IRHEESFNPLTCGFSLFFSLFS I 0 (SEQ ID NO:485); METLLLLLFFLSLLIFRFRILVSQCIN (SEQ ID NO:486); FLLTTVLLFSSKVRDP RANFDQSLRVLKHAKKVQPDVSKTSIMLGLGEND EQVYATMKGKEEEK (SEQ ID NO:487); and/or QQSCCFPVRFVILGPILISPYVY (SEQ ID NO:488). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in synovium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not lirruted to, arthritis and other diseases of the musculo-skeletal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculo-skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of diseases of the muscular-skeletal system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to

SEQ ID NO: 128 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 708 of SEQ ID NO: 128, b is an integer of 15 to 722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 128, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 119 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

I 0 VWLLSSELLRLVLWNRYTLQELSFWLPWFASRATSLVLQHG VLAMPF (SEQ ID NO:489);  
IRHEVSMFVFLAAGTLEPLYIAGA (SEQ ID NO:490);  
NSARGEYGFCLPSCSGYFGTAIHCRSLASGYHGLLPEQQA (SEQ ID NO:491)-, and/or  
HELTVP SRMGSKGKPYPCGFYSSLIP (SEQ ID NO:492). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in rejected kidney, stromal cells, and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the renal, central nervous and immune systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, renal and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., kidney, stromal cells, brain and other cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:268 as residues: Ser-6 to Arg The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the renal, central nervous, and immune systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases.

Some of these sequences are related to SEQ ID NO: 129 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 463 of SEQ ID NO: 129, b is an integer of 15 to 477, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 129, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 120 The protein of the invention has sequence identity to the *Saccharomyces cerevisiae* ankyrin repeat-containing protein (gil466522). Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

KCIYPKPARTHHCSICNRCVLKMDHHCPWLNNVCVGHYNHR  
CVYCSYGSWDLFREAYAAIIEKMKQLDKNKLQAVANQTYH (SEQ ID NO: 493);  
ARGHWNLILIVFHYYQAITTPPGYPPQGRNDIATVSIC (SEQ ID NO:494);  
WQCELD CVSHDSSTHSAPYVISRASKGSFSQNP (SEQ ID NO:495);  
SKRASGPALGYHAGQFKDQPFYHCRRTQCCEILGLTSLY  
GQAASYLPCPVLTRTSSRIQI-FWSWPPPLLLAV (SEQ ID NO:496); ESLQLRLLGQ  
LEGIPGCGYRKALAYSGALTF (SEQ ID NO:497); and/or SLAPWEWNELGA  
PSLGDCSLSLCDGSVSWTVSATRALILLPMLFQGPPRAA (SEQ ID NO:498). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in endometrial tumor and to a lesser extent in several other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of a number of types of cancers, particularly endometrial cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endometrium, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., endometrium and other reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:269 as residues: Asn-43 to Arg-49, Phe-57 to Cys-65, Pro-93 to Ser. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases and cancers of the endometrium and cancers of several different organs and tissue. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 130 and may have been publicly available prior to conception of the present invention.

Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is 1-5 any integer between 1 to 1282 of SEQ ID NO: 130, b is an integer of 15 to 1296, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 130, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 121** The translation product of this gene shares sequence homology with adrenalin receptor. Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

TATLNSFFGGWGLALLLRLECSDTIMDHCSLDLLGSSNPP HHAQLIFCFFVQTRSHSVA (SEQ ID NO:499); MDHCSLDLLGSSNPPASASQV VGTGARGHHAQLIFCFFVQTRSHSVA (SEQ ID NO:500); GVLKQSSHLVLSKG (SEQ ID NO:501); DYSCESLCPALLSIAPDIVLN (SEQ ID NO:502); TTIHKTQLGS YKILWEPKEGYHNSTWI (SEQ ID NO:503); IREIFLRPP (SEQ ID NO:504); and/or LKFQKPGKIQMRGGGRVFWYKNCK (SEQ ID NO:505). Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in synovial sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis and other diseases of the synovium including cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and muscular-skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to adrenalin receptor indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the synovium, immune system and musculo-skeletal system including cancers of these tissues and systems. It may also be useful for identifying and therapeutically using antagonists and agonists for this receptor family.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 131 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 724 of SEQ ID NO: 131, b is an integer of 15 to 738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 131, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 122 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

NSARVTQKGESVGSVCGMRAIAGFDNYPLF (SEQ ID NO:506);  
GTIGIFWPLPVAELSSGDYLQTIHRPLLHRT (SEQ ID NO:507); LPLPLSSLLHIATCNPFPKT (SEQ ID NO:508); SYFFVYNLILKIIQGDHASIILLATI PIFGDIYYVKGQLASFGPYL (SEQ ID NO:509);  
LFYHLEHSRHKSHCSIEA (SEQ ID NO:510); CSCHCPSRAFST (SEQ ID NO:511); and/or  
PHAIHSQKPSSIFLIT DVFPDPPVGIYLL (SEQ ID NO:512).

Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in chronic synovitis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory diseases and disorders of the musculo-skeletal system.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the inflammatory and musculo-skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., synovial tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the 15 disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:271 as residues: Ser-39 to Pro The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders and diseases of the inflammatory and musculo-skeletal system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 132 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 428 of SEQ ID NO: 132, b is an integer of 15 to 442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 132, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 123 Additional embodiments of the invention are directed to polypeptides comprising the following amino acid sequences.

RKLFHKINSKSFHLSGMHILISVWIVRSRIKVKYELL (SEQ ID NO:513)-I  
NSARDVFFTQKILYSQTCIFFPCLVPFSFLSFFFFLSFV (SEQ ID NO:514);  
MFSSLLKKFYILKHVYSFPVLHFLFFFLFSFSLSWAEKG TENCKMVKS (SEQ ID NO:515); and/or  
IQLLYLKGAAMKYLSYVARLLFLKALDLF APKMVQIDSF (SEQ ID NO:516).

Further embodiments of the invention are directed to polynucleotides which encode these polypeptides.

This gene is expressed primarily in kidney and infant brain and to a lesser extent in several other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the renal and central nervous systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the

tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., renal tissue, and brain and other cells and tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 272 as residues: Gly-24 to Lys-31.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the neural and renal systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO: 133 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 868 of SEQ ID NO: 133, b is an integer of 15 to 882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO: 133, and where b is greater than or equal to a + 14.

YNT NT 5' NT 3' NT of A@ ATCC SEQ of of 5' NT First SB Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. Codon Pep y I HCEIA77 209119 Uni-ZAP XR 11 1882 676 1882 785 785 15 06/12/97 2 HCFCEI0 209119 pSportl 12 1590 18 1590 198 198 15 06/12/97 3 HCFNC26 209119 pSportl 1 3 1373 6 1373 85 85 15 06/12/97 4 HCHAA63 209119 pSportl 1 4 1142 1 1142 130 130 15 06/12/97 5 HCNSP40 209119 pBluescript 1 5 1034 11034 106 106 15, 06/12/97 5 HCNSP40 209119 pBluescript 134 1032 1 1032 III 27 06/12/97 6 HDAACIO 209119 pSportl 1 6 1198 1 1198 117 117 1 5 06/12/97 7 HE8CV18 209119 Uni-ZAP XR 1 7 11447 1 1447 176 176 15i 06/12/97 8 HELDY05 209119 Uni-ZAP XR 1 8 1422 1 1375 79 79 15 06/12/97 9 HELDZ32 209119 Uni-ZAP XR 1 9 1107 1 2 1107 148 148 15@ 06/12/97 1 0 HFGALIO 209119 Uni-ZAP XR 20 1183 1 1183 179 179 15, 06/12/97 1 0 HFGALIO 209119 Uni-ZAP XR 13 5 1766 3 1765 1 79 179 27, 06/12/97 11 I HFK-EB72 209119 Fni-ZAP XR 2 1 1420 1 1 1420 43 43 161 06/12/97 5' NT NT 5' NT 3' NT of A@ ATCC SEQ of of 5' NT First SE ( Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. lCodon Pep I y 12 HFTCU 1 9 209119 Uni-ZAP XR 22 1575 1266 1575 137 137 16 06/12/97 12 HFTCU 1 9 209119 Uni-ZAP XR 136 470 1 470 157 157 27.

06/12/97 1 1 13 HFXHN31 209119 Lambda ZAP 23 541 541 172 172 16@ 06/12/97 II I 1 3 HFXHN31 209119 Lambda ZAP 13 7 1168 1 1168 293 293 27i 06/12/97 11 I 1 4 HGLAM53 209119 Uni-ZAP XR 24 83 3 219 83 3 359 3 59 16' 06/12/97 14 HGLAM53 209119 Uni-ZAP XR 1 3 8 1294 226 1288 3 69 27' 06/12/97 1 5 HJABB94 209119 pBluescript 25 1555 1 1555 74 74 16@ 06/12/97 SK- 16 HKIYO61 209119 pBluescript 26 1543 1 1543 181 181 16' 06/12/97 17 HLTA194 209119 Uni-ZAP XR 27 1262 1 1262 47 47 16( 06/12/97 1 8 HMDA151 209119 Uni-ZAP XR 28 753 1 753 12 12 16' 06/12/97 19 HMELRO3 209119 Lambda ZAP 29 1621 8 1535 200 200 16@ 06/12/97 11 20 HMKAHIO 209119 pSportl 30 921 1 921 48 48 16( 06/12/97 2 1 HMKCW19 209119 pSportl 3 1 2095 473 1934 529 529 17( 06/12/97 1 5' NT NT 5' NT 3' NT of A @ ATCC SEQ of of 5' NT First SD Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. Codon Pep y 21 HMKCW19 209119 pSportl 139 1720 103 1692 188 188 27 06/12/97 22 HMSJW18 209119 Uni-ZAP XR 32 1838 1 1838 28 28 17 06/12/97 23 HMWGYOI 209119 Uni-Zap XR 33 782 1 782 423 423 17 06/12/97 23 HMWGYOI 209119 Uni-Zap XR 140 774 1 774 17 17 27 06/12/97 24 HNFID82 209119 pBluescript 34 1560 1 1560 161 161 17 06/12/97 25 HNFID36 209119 pBluescript 35 1092 1 1082 171 171 17, 06/12/97 26 HNGEV29 209119 Uni-ZAP XR 36 11153 1 1153 173 173 17 06/12/97 26 HNGEV29 209119 Uni-ZAP XR 141 1566 1 1566 79 79 28, 06/12/97 27 HNGIK21 209119 Uni-ZAP XR 37 985 1 985 152 152 17, 06/12/97 28 HNGJJ65 209124 Uni-ZAP XR 38 1122 1 1122 84 84 17' 06/19/97 29 HNGJU42 209124 Uni-ZAP XR 39 598 6 598 273 273 17@ 06/19/97 30 HODAZ26 209124 Uni-ZAP XR 40 1129 8 1129 133 133 171 06/19/97 31 HODD1305 209124 Uni-ZAP XR 41 1 1 TT[-77 15 8 244 244 181 06/19/97 1 5' NT NT 5' NT 3' NT of A) ATCC SEQ of of 5' NT First SEI Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. Codon Pep y 32 HOFAP39 209124 pSportl 42 1767 1 1767 57 57 18 06/19/97 33 HOFNY71 209124 pCMVSPORT 43 917 1 917 114 114 18 06/19/97 2.0 34 HORB181 209124 Uni-ZAP XR 44 1987 8 1965 31 31 18 06/19/97 35 HOSCY73 209124 Uni-ZAP XR 45 j2O53 196 2048 209 209 18, 06/19/97 36 HPMBR15 209124 Uni-ZAP XR 46 11272 25 1272 262 262 18, 06/19/97 37 HSAVD46 209124 Uni-ZAP XR 47 773 2 767 173 18, 06/19/97 38 HSLBF69 209124 Uni-ZAP

XR 48 2119 1 2119 107 107 18' 06/19/97 39 HSOAH66 209124 Uni-ZAP XR 49 1188 7 1188 196 196 18.

06/19/97 39 HSOAH66 209124 Uni-ZAP XR 143 537 1 53 7 136 136 28@ 06/19/97 40 HSVBH58 209124 Uni-ZAP XR 50 478 24 155 249 249 181 06/19/97 40 HSVBH58 209124 Uni-ZAP XR 144 680 1 680 168 168 28'.

06/19/97 41 HSZAF47 209124 Uni-ZAP XR 5 1 1333 2 133 3 107 107 191 06/19/97 42 HTADV27 209124 Uni-ZAP XR 52 1255 1 14 112511 69 1 69 1 19 106/19/97 5' NT N T 5' NT 3' NT of A/ ATCC SEQ of o f 5' NT First SE( Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: N T Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. lCodon Pep l y 43 HTADX17 209124 Uni-ZAP XR 53 1140 22 1140 84 84 M 06/19/97 44 HTDAD22 209124 pSportl 54 1220 1 1220 193 193 19.

06/19/97 45 HTEDS39 209124 Uni-ZAP XR 55 694 198 694 205 205 194 06/19/97 45 HTEDS39 209124 Uni-ZAP XR 145 1048 1 1048 227 28d 06/19/97 46 HTEHH53 209124 Uni-ZAP XR 56 98 8 1 980 22 22 19@ 06/19/97 47 HTLDP69 209124 Uni-ZAP XR 57 1500 237 1500 330 330 19i 06/19/97 48 HTNBR95 209124 pBluescript 58 1391 1 13 86 70 70 19' 06/19/97 SK- 49 HTPCS60 209124 Uni-ZAP XR 59 1579 7 1259 105 105 M 06/19/97 50 HUKBHO5 209124 Lambda ZAP 60 1241 1 1215 151 151 191 06/19/97 II 5 1 HUKEX85 209124 Lambda ZAP 6 1 930 7 925 3 5 3 5 20( 06/19/97 11 5 1 HUKEX85 209124 Lambda ZAP 146 930 6 917 8 3 8 3 28' 06/19/97 II 52 HWTBM45 209124 Uni-ZAP XR 62 998 1 998 69 69 20' 06/19/97 5 3 HADFF38 219124 pSportl 63 1 11931 1 1 1034 1 64 1 06/19/97.

5' NT N T 5' NT 3' NT of A/ ATCC SEQ of of 5' NT First SE( Deposit ID Total Clone Clone of AA of IL Gene cDNA Nr and NO: N T Seq. Seq. Start Signal NO No. i Clone ID Date Vector X Seq. lCodon Pep l y 54 HADFK68 209124 pSportl 64 830 1 830 91 9 1 M 06/19/97 54 HADFK68 209124 pSportl 147 830 1 83 0 45 45 28i 06/19/97 1 55 HADGG19 209125 pSportl 65 867 1 867 262 262 20, 06/19/97 55 HADGG19 209125 pSportl 148 865 1 865 281 281 28' 06/19/97 56 HAEAV45 209125 pBluescript 66 685 46 647 487 487 20.

06/19/97 SK- 56 HAEAV45 209125 pBluescript 149 545 1 545 24 24 28@ 06/19/97 SK- 1 57 HARAA15 209125 pBluescript 67 801 1 801 185 185 20i 06/19/97 SK- 58 HATDL27 209125 Uni-ZAP XR 68 908 1 908 82 82 20' 06/19/97 59 HBFAQ54 209125 pSportl 69 696 209 696 229 229 201 06/19/97 60 HBGBA14 209125 Uni-ZAP XR 70 455 1 452 32 32 201 06/19/97 6 1 HBIAS26 209125 Uni-ZAP XR 7 1 413 1 3 72 57 57 21 ( 06/19/97 62 HBJFU48 209125 Uni-ZAP XR 72 849 1 849 20 20 21 06/19/97 63 HBJFV28 209125 Uni-ZAP XR 73 505 1 505 306 306 21, 06/19/97 5' NT NT 5' NT 3' NT of A@ ATCC SEQ of of 5' NT First SE( Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. lCodon Pep l y 64 HBMWBOI 209125 Uni-ZAP XR 74 719 1 719 48 48 2 1'.

06/19/97 65 HBMXN79 209125 Uni-ZAP XR 75 1274 141 974 192 192 21j 06/19/97 1 1 1 66 HBMXP84 209125 Uni-ZAP XR 76 1 519 1 5 19 161 161 2L 06/19/97 67 HCFMM26 209125 pSportl 77 3 89 1 3 89 178 178 21i 06/19/97 68 HCNAV36 209125 Lambda ZAP 78 823 411 823 505 505 21' 06/19/97 11 69 HCNSB01 209125 pBluescript 79 2455 533 1308 552 552 2U 06/19/97 70 HCRBR74 209125 Uni-ZAP XR 80 921 3 65 911 415 415 211 06/19/97 7 1 HCUBN59 209125 ZAP Express 8 1 678 1 678 96 96 22 ( 06/19/97 72 HCUDB38 209125 ZAP Express 82 857 1 j 857 221 221 22 06/19/97 73 HCUFZ62 209125 ZAP Express 83 1977 28 661 233 233 22, 06/19/97 1 74 HDHMB42 209125 pCMVSPORT 84 1149 427 1149 592 592 22' 06/19/97 2.0 75 HDPCO25 209125 pCMVSPORT 85 767 76 767 182 182 22@ 06/19/97 3.0 76 HDPH151 209125 pCMVSPORT 86 728 1 728 245 245 22A 06/19/97 3.0 5' NT NT 5' NT 3' NT of A) ATCC SEQ of of 5' NT First SE( Deposit ID Total Clone Clone of AA of IL Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID Date Vector X Seq. Codon Pep y 77 HE2EC79 209125 Uni-ZAP XR 87 735 1 73 5 151 151 22i 06/19/97 78 HE9FE83 209125 Uni-ZAP XR 88 889 332 889 3 5 1 351 22' 4 06/19/97 1 79 HE9HW52 209125 Uni-ZAP XR 89 569 73 569 122 122 22.

06/19/97 80 HEBFL88 209125 Uni-ZAP XR 90 334 2 334 76 76 221 06/19/97 81 HFIVB57 209125 pSportl 91 795 92 795 286 286 231 06/19/97 82 HFPDE69 209125 Uni-ZAP XR 92 5 77 1 577 72 72 23 06/19/97 83 HGBGV89 209125 Um-ZAP XR 93 968 1 968 55 55 23@ 06/19/97 84 HGLDE38 209125 Uni-ZAP XR 94 553 1 5 53 3 1 3 1 23 @ 06/19/97 85 I-IHGDU58 209125 Lambda ZAP 95 968 70 898 23 5 j 23 5 23 @ 06/19/97 11 86 HHTLF25 209125 ZAP Express 96 697 1 661 142 142 23' 06/19/97 87 HJMAV91 209125 pCMVSPORT 97 866 74 866 251 25 1 23( 06/19/97 3.0 88 HKAFB88 209125 pCMVSPORT 98 1368 219 795 23 8 23 8 23' 06/19/97 2.0 89 1 HLHFP03 209126 Uni-ZAP XR 99 613 1 613 224 224 23@ 06/19/97 1 5' NT NT 5' NT 3' NT of A) ATCC SEQ of of 5' NT First SE( Deposit ID Total Clone Clone of AA of 11 Gene cDNA Nr and NO: NT Seq. Seq. Start Signal NO No. Clone ID



Date Vector X Seq. Codon Pep y 90 HLNAB07 209126 Lambda ZAP 100 685 1 685 187 187 23 06/19/97 11 91  
HLWCF05 209126 pCMVSPORT 101 646 1 646 159 24 06/19/97 3.0 92 HLYAF80 209126 pSPORT 102 826 1 826 222  
222 24 06/19/97 93 HMDAA66 209126 Uni-ZAP XR 103 586 1 586 106 106 24 06/19/97 94 HMKDD07 209126  
pSPORT 104 628 43 628 267 267 24 06/19/97 95 HMKDS08 209126 pSPORT 105 558 1 558 230 230 24 06/19/97 96  
HMSHM14 209126 Uni-ZAP XR 106j 756 1 756 103 103 24 06/19/97 97 HMWDC28 209126 Uni-Zap XR  
10111146 105 754 124 124 24, 06/19/97 98 HNDAA54 209126 pCMVSPORT 108 775 1 775 26 26 24 06/19/97 2.0 1  
99 HNFDS53 209126 Uni-ZAP XR 109 911 1 911 200 200 24@ 06/19/97 100 HNFUI96 209126 pBluescript 110 456  
1 456 170 170 24, 06/19/97 101 HNGAC63 209126 Uni-ZAP XR 111 554 1 554 214 214 25i 06/19/97 102  
HNGAX58 1 209126 F@ @-ZAP @XR 1121 7-22 1 722 100 100 25 1 06/19/97 5'NT NT 5' NT 3' NT of A) ATCC  
SEQ of of 5' NT First SB Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq. Start  
Signal NO No. Clone ID Date Vector X Seq. Codon Pep y 103 HNGEM24 209126 Uni-ZAP XR 113 931 1 931 239  
239 25 06/19/97 104 HNGFT78 209126 Uni-ZAP XR 114 588 1 588 20 20 25 06/19/97 105 HNHD185 209126  
Uni-ZAP XR 115 812 1 812 194 194 25 06/19/97 1 1 106 HNHFU59 209126 Uni-ZAP XR 116 506 1 506 278 278  
25 06/19/97 107 HNHFU22 209126 Uni-ZAP XR 117 751 1 751 228 228 25 06/19/97 108 HOAAF80 209126  
Uni-ZAP XR 118 960 131 960 303 25 06/19/97 109 HODCJ90 209126 Uni-ZAP XR 119 1442 326 1133 344 344 25  
06/19/97 110 HOECO90 209126 Uni-ZAP XR 120 845 215 845 299 299 25 06/19/97 111 HPEBT80 209126 Uni-ZAP  
XR 121 360 1 360 2 1 2 1 26, 06/19/97 112 HSDAGO5 209126 Uni-ZAP XR 122 944 231 848 419 419 26 06/19/97  
113 HSDGR57 209126 Uni-ZAP XR 123 914 115 914 195 195 26 06/19/97 114 HSDJJ82 209126 Uni-ZAP XR 124  
462 1 462 79 79 26.

06/19/97 1 115 HSDZM95 209126 pBluescript 125 545 1 145 223 223 26j 06/19/97 5' NT NT 5' NT 3' NT of AY  
ATCC SEQ of of 5' NT First SEI Deposit ID Total Clone Clone of AA of IE Gene cDNA Nr and NO: NT Seq. Seq.  
Start Signal NO No. Clone ID Date Vector X Seq. Codon Pep y 116 HSD115 209126 Uni-ZAP XR 126 912 1 873  
173 26, 06/19/97 117 HSKYU29 209126 pBluescript 127 1048 1 1047 290 290 26, 06/19/97 118 HSNA55 209126  
Uni-ZAP XR 128 722 1 722 35 35 26' 06/19/97 119 HSQFP66 209126 Uni-ZAP XR 129 477 1 477 96 96 26.

06/19/97 120 HSRDE35 209126 Uni-ZAP XR 130 1296 232 804 428 428 26, 06/19/97 121 HSSJN64 209126  
Uni-ZAP XR 131 738 1 738 70 70 271 06/19/97 122 HSVAQ28 209126 Uni-ZAP XR 132 442 1 442 149 149 27  
06/19/97 HSVAY16 209126 Uni-ZAP XR 133 882 1 790 52 52 27.

06/19/97 Table I summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NOX" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table I and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NOX. The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NOX. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep." The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the

invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by 15 sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein.

Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988).

Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

Signal Sequences Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the

range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10: 1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty.

Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence.

However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are.

Matrix=Unitary, k-tuple=4, Mismatch Penalty= 1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score= 1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of

the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table I or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences.

The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty= 1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score= 1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C- terminal truncations of the subject sequence when calculating global percent identity.

For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence.

This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level.

Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).) Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine EL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc: fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).) Polynucleotide and Polypeptide Fragments In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NOX The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NOX These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401 - 450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NOX or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NOX or

encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred.

Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Particularly, N-terminal deletions of the polypeptide of the present invention can be described by the general formula m-p, where p is the total number of amino acids in the polypeptide and m is an integer from 2 to (p-1), and where both of these integers (m & p) correspond to the position of the amino acid residue identified in SEQ ID NO: Y.

Moreover, C-terminal deletions of the polypeptide of the present invention can also be described by the general formula I-n, where n is an integer from 2 to (p-1), and again where these integers (n & p) correspond to the position of the amino acid residue identified in SEQ ID NO: X.

The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: X, where m and n are integers as described above.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

Polypeptide fragments of SEQ ID NO: X falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

**Epitopes & Antibodies** In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).) Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.) In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).) Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes



may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.) As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody.

(Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library.

Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

**Fusion Proteins** Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4- polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J.

Biochem. 270:3958-3964 (1995).) Similarly, EP-A-0 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, WO 99/02546 PCT/US98/13684 167 Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol.

Chem. 270:9459-9471 (1995).) Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available.

As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein.

Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).) Thus, any of these above fusions can be engineered using

the polynucleotides or the polypeptides of the present invention.

**Vectors, Host Cells, and Protein Production** The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH 1 6a, pNH I 8A, pNH46A, available from Stratagene Cloning Systems, Inc.; and I 0 ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLN'EO, pSV2CAT, pOG44, pXT 1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

**Uses of the Polynucleotides** Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO: X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO: X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined.

First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a nonnal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class H HLA gene, are used in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class H HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type.

In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to it subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985)-Jalkanen, M., et al., J. Cell. Biol. 105:3087- 3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (I 251, I 125), carbon (14C), sulfur (35S), tritium (3H), indium (111In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 125I, 111In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).) Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease.

For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

**Biological Activities** The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Actiyfty A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells 1 5 from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to.

blood protein disorders (e.g. aganimaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an

inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischaemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.) Hyperproliferative Disorders A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picomaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-1, HTLV-11, Lentivirus), and Togaviridae (e.g., 5 Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillois, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g.,



Actinobacillus, Hearnophilus. Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections.

A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas.

These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and 15 peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy- Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

**Chemotaxis** A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body.

For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

**Binding Activity** A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e. a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., *Current Protocols in Immunology* 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*.

Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b)

determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with 1-5 a polypeptide of the invention, (b) assaying a biological activity, and (c) determining if a biological activity of the polypeptide has been altered.

**Other Activities** A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

**Other Preferred Embodiments** Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X. Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X. A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X. Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone

identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table I for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide 1-5 sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide

sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO: X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO: Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO: Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO: Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO: Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO: Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO: Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in

Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table I and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table I and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples Example 1: Isolation of a Selected cDNA Clone From the Deposited SanWle Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector.

1 5 Table I identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table I as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript." Vector Used to Construct Librgy Corresponding Deposited Plasmid Lambda Zap pBluescript (pBS) Uni-Zap XR pBluescript (pBS) Zap Express pBK lafmid BA plafmid BA pSportl pSportl pCMVSPORT 2.0 pCMVSPORT 2.0 pCMVSPORT 3.0 pCMVSPORT 3.0 pCRO2.1 pCRO2.1 Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos.

5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res.

16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., Nucleic Acids Res.

17:9494 (1989)) and pBK (Altling-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forins SK+, SK-, KS+ and KS.



The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain 1013111013, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCRg2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9.

(1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table I for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table I. Typically, each ATCC deposit sample cited in Table I comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO: X. Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with 3'- $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above.

The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate.

These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO: X (i.e., within the region of SEQ ID NO: X bounded by the 5'NT and the 3'NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25  $\mu$ mol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript.

(Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).) Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

**Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide** A human genomic PI library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NOX, according to the method described in Example 1. (See also, Sambrook.) **Example 3: Tissue Distribution of Polypeptide** Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprimeTm DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-IOTM column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT 1200- 1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

**Multiple Tissue Northern (MTN) blots** containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHybTm hybridization solution (Clontech) according to manufacturer's protocol number PT I 190- 1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

**Example 4: Chromosomal Mapping of the Polynucleotides** An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NOX. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions: 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions are analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

**Example 5: Bacterial Expression of a Polypeptide** A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB

plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml).

The O/N culture is used to inoculate a large culture at a ratio of 1: 100 to 1:250. The cells are grown to an optical density 600 (O.D .600) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM.

IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HO by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., supra). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., supra).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M- 1 M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors.

The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Iminidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgamo sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriQ is derived from pUC 19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

**Example 6: Purification of a Polypeptide from an Inclusion Body** The following alternative method can be used to purify a polypeptide expressed in E coli when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4- 10°C.

Upon completion of the production phase of the E. coli fermentation, the cell culture is cooled to 4- 10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit 5 weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7. The cells are dispersed to

a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7. The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored.

Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6. Fractions are collected under constant A280 monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded.

The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

**Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System** In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from E. coli under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence,

using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

15 The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. E. coli HB 101 or other suitable E. coli hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added.

Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, supra. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a plaque assay of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200  $\mu$ l of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5  $\mu$ Ci of <sup>35</sup>S-methionine and 5  $\mu$ Ci <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

**Example 8: Expression of a Polypeptide in Mammalian Cells** The polypeptide of the present invention can be expressed in a mammalian cell.

A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the

transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV1, HIV1 and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC I -3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., *J. Biol. Chem.* 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., *Biochem. et Biophys. Acta*, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., *Biotechnology* 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., *Biochem J.* 227:277-279 (1991); Bebbington et al., *Bio/Technology* 10: 169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell* 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.) The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB 101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for 5' transfection. Five µg of the expression plasmid pC6 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., supra). The plasmid pSV2-neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418.

After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1.4M 9.2 gM 9.5 @tM@ 10 mM 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 gM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

**Example 9: Protein Fusions** The polypeptides of the present invention are preferably fused to other proteins.

These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.) Human IgG Fc region.

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACACACATG
CAGCACCTGAATTCGAGGGTGACCGTCAGTCTTCCTCTT
CAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACA
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGA
AGCACGTACCGTGTGGTCAGCGTCCTACCGTCCTGCACC
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAAC
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCC
GAGCAATGGGCAGCCGAGAACAACTACAAGACCACGCCT
ACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGT
GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGG GACGGCCGCGACTCTAGAGGAT (SEQ ID
NO: 1) 5
```

**Example 10: Production of an Antibody from a Polypeptide** The antibodies of the present invention can be prepared by a variety of methods.

(See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted I 0protein is prepared and purified to render it substantially free of natural contaminants.

Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.



In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., *Nature* 256:495 (1975); Köhler et al., *Eur. J. Immunol.* 6:511 (1976); Köhler et al., *Eur. J.*

*Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 gA of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 gg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide.

Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art.

(See, for review, Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., *U.S. Patent No. 4,816,567*; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 870267 1; Boulianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985).) Example 11: Production Of Secreted Protein For High-Throughput Screening Assays The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13 First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a WO 99/02546 PCT/US98/13684 204 Plate 293T cells (do not carry cells past P+20) at 2 x 10<sup>5</sup> cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimum 1 (31985070 Gibco/BRL)/96-well plate.

With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimum 1 mixture to each well.

Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimern I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with 1ml PBS. Person A then aspirates off PBS rinse, and person B, using a channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectan-tine/Optimern I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37C for 6 hours.

While cells are incubating, prepare appropriate media, either 1 %BSA in DMEM with 1 x penstrep, or CHO-5 media (16.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CUSO<sub>4</sub>-5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub> ·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>-7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub> ·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HP0<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>-7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L-Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL ·H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 11.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of 10 Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20mM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mM glutamine and 1x penstrep. (BSA (813 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13. It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

**Example 12: Construction of GAS Reporter Construct** One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class 1, cells after treatment with IL-12. Stat5 was originally called mammary growth factor,

but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621- 51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class I includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL- 11, IL- 12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL- 10. The Class I receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

JAKs STATs GAS(elements) or ISRE Ligand jyk2 Jak I Jak2 Jak3 IFN family IFN-a/B + + 11213 ISRE IFN-g + + - I GAS (IRF1>Lys6>IFP) II-lo + ? ? - 113 g12130 family EL-6 (Pleiotrohic) + + + ? 193 GAS (IRF1>Lys6>IFP) II- 11 (Pleiotrohic) ? + ? ? i@3 OnM(Pleiotrohic) ? + + ? 113 LIF(Pleiotrohic) ? + + ? 113 CNTF(Pleiotrohic) -/+ + + ? 113 G-CSF(Pleiotrohic) ? + ? ? 1 73 IL-12(Pleiotrohic) + + + i,3 g-C family IL-2 (lymphocytes) - + + 1 9315 GAS EL-4 (lymph/myeloid) - + + 6 GAS (IRF 1 IFP >>Ly6)(IgH) IL-7 (lymphocytes) - + + 5 GAS IL-9 (lymphocytes) - + + 5 GAS EL-13 (lymphocyte) - + ? ? 6 GAS IL- 1 5 ? + ? + 5 GAS a12140 family IL-3 (myeloid) + - 5 GAS (IRF1>IFP>>Ly6) EL-5 (myeloid) + - 5 GAS GM-CSF (myeloid) + - 5 GAS Growth hormone family GH ? + - 5 PRL ? + - 11315 EPO ? + - 5 GAS(B-CAS>IRF1=IFP>>Ly6) Receptor Tyrosine Kinases EGF ? + + - 113 GAS (IRF I) PDGF ? + + - 173 CSF-1 ? + + - 1@3 GAS (not IRF1) To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is.

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAAT  
AAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3) The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5': GCGGCAAGCTTTTGGCAAAGCCTAGGC:3'(SEQ ID NO:4) PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence.

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATT  
ATTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACC  
CTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCG  
CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGA  
CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGGA TGCAAAAAGCTT:3' (SEQ ID NO:5) With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly,however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green

fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEA-P-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13. Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16.

However, many other promoters can be substituted using the protocols described in these Examples. For instance, SIZE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter 15 construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

#### Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12.

Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TEB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4<sup>+</sup> Th 1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200  $\mu$ l of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1  $\mu$ g/ml Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10  $\mu$ g of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50  $\mu$ l of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10<sup>6</sup> per transfection), and resuspend in OPTI-MEM to a final concentration of 1  $\times$  10<sup>6</sup> cells/ml. Then add 1 ml of 1  $\times$  10<sup>6</sup> cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel

pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -200C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 40C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

**Example 14: High-Throughput Screening Assay Identifying Myeloid Activity** The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells.

Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEA-P activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2x10<sup>7</sup> U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na<sub>2</sub>HPO<sub>4</sub>·7H<sub>2</sub>O, 1 mM MgCl<sub>2</sub>, and 675 uM CaCl<sub>2</sub>. Incubate at 370C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 370C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting 1x10<sup>6</sup> cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5x10<sup>5</sup> cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1x10<sup>6</sup> cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11.

Incubate at 370C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

**Example 15: High-Throughput Screening Assay Identifying Neuronal Activity**

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC 12 cell lines. PC 12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC 12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC 12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol.

The EGR-1 promoter sequence (-633 to +1) (Sakamoto K et al., *Oncogene* 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers.

5'GCGCTCGAGGGATGACAGCGATAGAACCCCGG -Y (SEQ ID NO:6)  
5'GCGAAGCTTCGCGACTCCCGGATCCGCCTC-3' (SEQ ID NO:7) Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two n-ds of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 n-J per well of the 96-well plate, and allowed to air dry for 2 hr.

PC 12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC 12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC 12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC 12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF-KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I-KB is phosphorylated and degraded, causing NF-KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF-KB include IL-2, IL-6, GM-CSF, ICAM-1 and class I MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO: 8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site.

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACT TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9) The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site.

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3'(SEQ ID NO:4) PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence.

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCG  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCC  
TCCCGCCCCCTAACTCCGCCCCAGTTCCGCCCCATTCTCCGCC  
AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCC  
CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTT.

3'(SEQ ID NO:10) Next, replace the SV40 minimal promoter element present in the pSEAP2- promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and HindIII.

However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes Sall and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP- I (Clontech), replacing the GFP gene, after restricting pGFP- I with Sall and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (O. 1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5- 10 fold activation typically observed.

Example 17: Assay for SEAP Activity As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15  $\mu$ L of 2.5x 10 dilution buffer into Optiplates containing 35  $\mu$ L of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50  $\mu$ L Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50  $\mu$ L Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in



chemiluminescence indicates reporter activity.

#### Reaction Buffer Formulation.

#of plates Rxn buffer diluent (ml) CSPD LMI) 60 3 1 1 65 3.25 70 3.5 75 3.75 80 4 85 4.25 90 4.5 95 4.75 1 8 100 5 105 5.25 110 5.5 115 5.75 120 6 125 6.25 130 6.5 135 6.75 140 7 145 7.25 150 7.5 155 7.75 160 8 3 1 165 8.25 170 8.5 175 8.75 180 9 185 9.25 190 9.5 195 9.75 200 10 205 10.25 210 10.5 215 10.75 220 1 1 225 11.25 230 11.5 235 11.75 240 12 245 12.25 250 12.5 255 12.75 260 1 3 Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours.

The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is incubated at 37C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.

The tube is then placed in a 37C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family. members of which mediate signal transduction triggered by

the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200n-fl/well) and cultured overnight in complete medium.

Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50  $\mu$ l of the supernatant produced in Example 1, the medium was removed and 100  $\mu$ l of extraction buffer ((20 mM HEPES pH 7.3, 150 mM NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 40°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45  $\mu$ m membrane bottoms of each well using house vacuum.

Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 40°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10  $\mu$ l of 5  $\mu$ M Biotinylated Peptide, then 10  $\mu$ l ATP/M92+ (5mM ATP/50mM M902), then 10  $\mu$ l of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1 mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5  $\mu$ l of Sodium Vanadate(1mM), and then 5  $\mu$ l of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initiate the reaction by adding 10  $\mu$ l of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10  $\mu$ l of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50  $\mu$ l aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide.

Wash the MTP module with 300  $\mu$ l/well of PBS four times. Next add 75  $\mu$ l of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5  $\mu$ g/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation ActiyRI As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk- 1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tee, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk- 1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1 ml of protein G (1 µg/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100 ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 40C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 1 1 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (100 ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1 µg/ml) which specifically recognizes the phosphorylated epitope of the Erk- 1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NOX Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60- 120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiThermin Polymerase. (Epicentre Technologies).

The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenin deoxy-uridine 5'- triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot- 1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino phenylidole and 1.5 propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv.

et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

**Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample** A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 µg/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide.

Next, 50 µl of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature.

The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

Add 75 µl of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale).

Interpolate the concentration of the polypeptide in the sample using the standard curve.

**Example 23: Formulating a Polypeptide** The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the human. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic

solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules.

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., *Biopolymers* 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and R. Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (+3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both.

Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol, or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1 - 10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile.

Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture is

lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

**Example 24: Method of Treating Decreased Levels of the Polypeptide** It will be appreciated that conditions caused by a decrease in the standard or nonnal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form.

Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1 - 100 ug/kg of the polypeptide for six consecutive days. Preferably, the 10 polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

**Example 25: Method of Treating Increased Levels of the Polypeptide** Antisense technology is used to inhibit production of a polypeptide of the 15 present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

**Example 26: Method of Treatment Using Gene Therapy** One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37C for approximately one week.

At this time, fresh media is added and subsequently changed every several days.

After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB 101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am I 2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Method of Treatment Using Gene Therapy - In Vivo Another aspect of the present invention is using in vivo gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide of the present invention. A polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the encoded polypeptide by the target tissue.

Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther.

3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs of the present invention may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). These polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs of the present invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the present invention can be delivered to the interstitial space of tissues within the animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the



space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg.

Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose.

In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle in vivo is determined as follows. Suitable template DNA for production of mRNA coding for the polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15  $\mu$ m cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA of the present invention.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference.

Further, the Sequence Listing submitted herewith in paper and computer readable forms are herein incorporated by reference in their entireties.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM (PCT Rule 13bis) A. The indications made below relate to the microorganism referred to in the description on page 143 line N/A B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet Name of depositary institution American Type Culture Collection Address of depositary institution (including postal code and country) 10801 University Boulevard

Manassas, Virginia 20110-2209 United States of America Date of deposit Accession Number 209119 June 12, 1997  
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet  
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13111@1 F1 Authorized officer L INDICATIONS RELATING TO A DEPOSITED MICROORGANISM (PCT Rule 13bis) A. The indications made below relate to the microorganism referred to in the description on page 145 line N/A B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet Name of depositary institution American Type Culture Collection Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America Date of deposit June 19, 1997 Accession Number 209124 C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit") For receiving Office use only For International Bureau use only This sheet was received with the international application This sheet was received by the International Bureau on.

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1 An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of- (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence

included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity; (f) a polynucleotide which is a variant of SEQ ID NO:X; (g) a polynucleotide which is an allelic variant of SEQ ID NO:X; (h) a polynucleotide which encodes a species homologue of the SEQ ID NO: Y; (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues. 2 . The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein. 3 . The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NOX 4 The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NOX 5 The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N- terminus. 6 . The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N- terminus.

7 A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8 A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9 A recombinant host cell produced by the method of claim 8.

10 The recombinant host cell of claim 9 comprising vector sequences.

11 An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of- (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity; (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (d) a polypeptide epitope of SEQ ID NO: Y or the encoded sequence included in ATCC Deposit No:Z; (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (g) a variant of SEQ ID NO:Y; (h) an allelic variant of SEQ ID NO:Y; or (i) a species homologue of the SEQ ID NO:Y.

12 The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13 An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14 A recombinant host cell that expresses the isolated polypeptide of claim 11.

15 A method of making an isolated polypeptide comprising: (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and (b) recovering said polypeptide.

16 The polypeptide produced by claim 15.

17 A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18 A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising: (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19 A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising: (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the

presence or amount of expression of the polypeptide.

20 A method for identifying a binding partner to the polypeptide of claim 11 comprising: (a) contacting the polypeptide of claim 11 with a binding partner; and (b) determining whether the binding partner effects an activity of the polypeptide.

21 The gene corresponding to the cDNA sequence of SEQ ID NO: Y.

22 A method of identifying an activity in a biological assay, wherein the method comprises: (a) expressing SEQ ID NOA in a cell; (b) isolating the supernatant; (c) detecting an activity in a biological assay; and (d) identifying the protein in the supernatant having the activity.

23 The product produced by the method of claim 22.

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